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CAVALCADE OF SOME HORMONES AND STEROIDS

EDWARD C. KENDALL, Ph.D.
Princeton, New Jersey

IN BIOCHEMISTRY, the years between 1900 and 1950 record the discovery of vitamins and hormones. These compounds, first recognized only by their physiological effects, gradually were isolated in pure crystalline form. The chemical structure of each one was determined, and all but a very few have been prepared by synthesis.

In medicine, the same half century marked the recognition of serum disease, hypersensitivity, immunity, anaphylaxis, and allergy.

Those who worked in biochemistry and investigators in experimental biology slowly have built up a fund of knowledge which has helped to explain the nature of allergic reactions and has afforded a measure of treatment. Finally, these results have been extended to a study of allergy in the field of clinical medicine. For the clinical investigator, nature has supplied an infinite variety of allergic conditions, and in recent years the chemist has furnished an impressive array of new compounds. In retrospect, the passing decades present a cavalcade of progress toward complete understanding.

But to an observer of this procession, it is apparent that there are distinctly different units throughout the parade. There are sharply defined segments of chemists, physiologists, experimental surgeons, clinical investigators, allergists and general practitioners. Each unit speaks a different language and deals with quite different materials.

It is an honor for one who has worked in a field outside of your own to be chosen as your guest speaker. I am mindful that, quote, "As chemists, we concern ourselves with the collisions of molecules and ions and

Dr. Kendall is Visiting Professor in Chemistry, Princeton University, Princeton, New Jersey.

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the breaking and mending of chemical bonds, while lawyers and doctors are concerned with collisions of automobiles and the breaking and mending of human limbs. Certainly law and medicine will always be closer to the personal lives of people than is chemistry."

But I am sure that there is no thought of rivalry. The chemist is comfortable in the laboratory where he can utilize his creative ability. He would be wholly unprepared to carry the responsibilities of clinical medicine. On the other hand, few physicians could diagnose a broken chemical bond and fewer still could mend one. It is not my purpose to suggest a change in the status quo, but to emphasize the advantage of co-operation between chemists and allergists. This has been fruitful in the past and holds the key to future progress.

In the cavalcade of hormones, the first ductless gland to attract the attention of chemists was the adrenal. In 1901, epinephrine was isolated in crystalline form by Takamini.

Epinephrine was separated from bovine adrenal glands for the following thirty-three years by a method which afforded this hormone as the sole product of the gland. In 1934, McKenzie and I at the Mayo Foundation devised a method by which the cortical adrenal hormones were separated as the principal product and epinephrine was a by-product. This is an unimportant footnote in the history of epinephrine, but to us it was a key which unlocked an inexaustible reservoir of adrenal glands. During fifteen years we were given without cost, a total of 150 tons of adrenal glands. In return for this we separated epinephrine valued at more than $9,000,000.00.

There are two items of interest. The first is that the method we devised for isolation of epinephrine, as a by-product, gave a higher yield and material of greater purity than did the old method. The second item concerns the high blood pressure associated with pheochromocytoma. Dr. Russel Wilder requested me to see if such a tumor, which had been removed at operation, contained epinephrine. Through use of the new method, I isolated almost one gram of what appeared to be pure epinephrine. I believe this was the first time that this hormone was isolated from such a tumor.

But now I must report to you that the facts just recited were subsequently shown to be but the first approach to the final truth. After we had completed our work with epinephrine, Tullar showed in 1949 that the adrenal medulla elaborates a second hormone, norepinephrine. These hormones are present in the proportion of about five parts of epinephrine to one of norephinephrine. Furthermore, in pheochromocytoma, Goldenberg and his co-workers found that the ratio of epinephrine to norephinephrine is about 1:9.

This same type of stepwise revelation has occurred with all the other hormones, and it was this pattern of progress that suggested to me the word cavalcade.

The second ductless gland to yield its secret to the chemist was the thyroid. Baumann in 1895 reported that iodine was combined with an organic compound, but this substance eluded isolation for nineteen years. It was then separated by your speaker and named thyroxin, but its chemical structure was not established until twelve more years had passed. C. H. Harington identified and synthesized this hormone. Thyroxin contains four atoms of iodine and for the following twenty-six years was believed to be the only physiologically active iodine-containing compound in the thyroid gland.

A second hormone, identical with thyroxin but with three instead of four atoms of iodine, was isolated by Pitt-Rivers in 1952. This was shown to act in the same manner as thyroxin but more promptly and for a shorter time. This advance was followed by preparation of many derivatives, but the end has not been reached.

Sixty-five years now have passed, but the mechanism by which thyroxin influences the animal organism cannot yet be stated in terms of chemistry.

The last two hormones to be mentioned are ascorbic acid and cortisone. Saint Gyorgyi isolated the first small amount of ascorbic acid from bovine adrenal glands at Cambridge, England. This first sample was large enough to determine its composition but not its chemical structure. The compound had interesting chemical properties, but at that time its biological importance was not known. The first large sample was prepared by Saint Gyorgyi in my laboratory at the Mayo Foundation in 1929. Saint Gyorgyi sent several grams of the compound to Professor Haworth at Manchester, England. Haworth was an eminent chemist who had worked in the field of sugars. He had agreed to determine the chemical structure of the new substance but for some reason, not known to me, he postponed the work for no less than two years.

Meanwhile Saint Gyorgyi showed that his new compound and vitamin C were one and the same. This precipitated a rush to establish the chemical structure of vitamin C. Within a short time the exact structure was determined and the vitamin was synthesized by Reichstein and co-workers.

Man, monkeys and guinea pigs are the only animals known that cannot make ascorbic acid. For these, the compound is a vitamin and must be taken into the body from an outside source. For all other animals, it is a hormone which is elaborated within the body.

The last and the most important hormone from the standpoint of the allergist is cortisone. I shall use this word in a generic sense to include the derivatives of this compound. Time does not permit a detailed recitation of the stormy career of this hormone from its isolation as compound E in my laboratory in 1935 to its culmination under the designation of cortisone at the seventh International Congress of Rheumatologists in New York City in June, 1949. But there are several phases of the investigation which were dramatic and filled with human import.

There were three aspects of the study of the adrenal cortex which set

it apart from all the other hormones. The first was clarification. Following 1930, when active extracts of the adrenal cortex were made available through the work of Swingle and Pfiffner at Princeton and Hartman and his co-workers at Buffalo, ten years of uninterrupted research were required to show that not one but two hormones were needed to explain the significance of the adrenal cortex. One hormone now known as aldosterone was required to control mineral metabolism but in addition, compound E was essential to restore to normal a patient who had Addison's disease.

The second reason which made the adrenal cortex of special interest was the limited source of the cortical hormones. It was clearly obvious that the adrenal glands of cattle could not furnish enough starting material to supply the probable demand, and that some other source from plants or animals was essential.

The third aspect, characteristic of the adrenal cortex, was the limited information in 1940 concerning the chemistry of the steroid family of compounds. The synthesis of compound E from some abundant steroid starting material was a reasonable program. But synthesis alone was not enough. Whatever method was devised, it would be necessary to prepare the hormone at a price which would permit its use in clinical medicine.

The synthesis of compound E was placed at the top of the agenda of the National Research Council in October, 1941 as a war measure. Even with this moral and financial support, the problems proved to be insurmountable. The project was terminated by the National Research Council in 1944. Merck and Company and my laboratory at the Mayo Foundation were the only places to continue work toward a practical synthesis of the hormone. Each laboratory was independent, and each one made essential contributions. In the spring of 1948, the first small trickle of compound E became available but by that time almost everyone had lost interest in the hormones of the adrenal cortex.

I have described the chemical section of the cavalcade of hormones and have pointed out the slow accretion of knowledge concerning them. Recognition and effective treatment of allergic conditions has followed a course which is quite similar. You are more familiar with the development of the study of allergy than I am, but we meet on common ground in the therapeutic use of the hormones.

Four years after epinephrine became available, it was found to be effective in the treatment of asthma and other allergic conditions. These results often were dramatic and were among the most striking observations in the field of clinical medicine. However, in many cases, relief of symptoms was short lived. Twenty-three years passed before methods were discovered by which the beneficial effects of epinephrine could be prolonged.

All who are interested especially in the treatment of allergic disorders will recognize that epinephrine is still one of the most valued and widely employed therapeutic agents in the field of allergy.

To the present time thyroxin has not been of value to the allergist. In the text book *Allergy in Practice,* Feinburg makes the statement, "In my experience thyroid medication has no place whatsoever in allergy." I shall not dispute this but will refer again to some recent work with thyroxine and its derivatives.

For the treatment of allergic conditions, ascorbic acid fares no better than thyroxin and has been shown to be essentially worthless for the relief of hay fever and asthma. Again I shall postpone discussion of the action of ascorbic acid to a later paragraph. At this time I shall make the observation that no close relative of ascorbic acid has yet been made which has physiologic activity. Perhaps such compounds will be made available through further investigation by the chemist.

The utilization of the hormones of the adrenal cortex in clinical medicine is widely different from that of epinephrine in respect to time. There was a gap of thirteen years between the date of isolation of compound E and its first use in clinical medicine, but the only reason for this delay was availability. Compound E never was isolated from the adrenal glands in amount sufficient to permit a clinical investigation of its activity.

Compound E probably would have been left on the shelf for a long time after it had been prepared on a large scale except for the curiosity and diligence of one man. May I remind you of the long search by Dr. Philip S. Hench for some compound that could hold in check the progress of the distressing symptoms of rheumatoid arthritis. At a conference in January, 1941, Dr. Hench and I decided to try compound E in the treatment of rheumatoid arthritis, but we did not realize that almost eight years would pass before that hormone would be available.

You know the result of that investigation by the team of Hench, Slocumb, Polley and Kendall. It is fortunate that the disease which we studied was rheumatoid arthritis. If it had been Addison's disease it would have attracted little attention. The announcement that the symptoms of rheumatoid arthritis could be relieved was front page news, and resulted in widespread interest among clinical investigators, pharmaceutical manufacturing companies, and hopeful patients.

No time was lost by the clinicians. Cortisone was tried in the treatment of almost every known disease. This created an enormous demand for the hormone, and this in turn was a major stimulus for research in chemical laboratories. At first the objective was to make cortisone, to raise the yield, and to lower the price as fast as possible. There was strong competition. Within a short time, but after much intensive work, hydrocortisone became available.

For both clinicians and chemists, this seemed to be the end. The hormones elaborated by nature now had been duplicated. They were available at a reasonable price and in any desired quantity. Could anything more be expected? To the chemist it was obvious that a large number of derivatives of the steroid nucleus could be prepared. To the clinician it was clear

that these new compounds could be compared with cortisone or hydrocortisone both on a qualitative and a quantitive basis.

The pharmaceutical companies were willing to provide the research, and quantities of the new compounds for clinical testing, but for them this program was a variation of that old game of musical chairs. When the music stopped, and everyone sat down in the nearest chair, would they find themselves comfortably seated with a bright and prosperous future, or would they be left standing with empty hands?

This interesting pursuit has been in progress for almost ten years and has provided new tools for the clinician. Not only new compounds, but of still more importance, new methods to study the distribution, the excretion, and the metabolism of the cortical hormones have been devised. These new techniques which employ trace amounts of radio-active material and separations based on chromotography would have been regarded as fantastic and forever impossible just a few years ago. This new chapter in biochemistry has resulted in an enormous addition to our knowledge of the chemistry of the steroids and finally, it has been profitable for some pharmaceutical companies.

I shall avoid the political and economic aspects of research by pharmaceutical companies and shall summarize the scientific contributions concerned with steroids. Three different types of physiological activity have been followed. These are (1) the metabolism of electrolytes, (2) the metabolism of carbohydrates, and (3) anti-inflammatory activity. It was soon found that steroids which caused retention of sodium were not satisfactory, and that usually there was a good correlation between the influence on carbohydrate metabolism and the anti-inflammatory action.

As early as 1953, Fried and Sabo discovered that substitution of cortisone with halogen, at position nine, increased the anti-inflammatory action, but also caused a marked retention of sodium. The advantage conferred in the desired direction was counterbalanced by the undesirable influence.

The year 1954 marked the preparation of prednisone and prednisolone. These compounds were not produced through foresight or intention. They were formed from cortisone and hydrocortisone by the action of bacteria which had been employed originally for quite a different purpose. Although this result was fortuitous, the new compounds promptly were manufactured on a large scale and were introduced as new therapeutic agents. These derivatives were slight modifications of the original hormones. They had but small influence on the retention of sodium, but the anti-inflammatory effect was much increased.

A study of these and other modifications of the steroid nucleus showed conclusively that two of the physiologic properties of cortisone could be dissociated one from the other. The influence of the steroid on mineral metabolism and the anti-inflammatory action were found to be separate effects. Either one could be increased or decreased independently of the

other. These facts provided a pattern or scheme for research which has been followed by chemists in many pharmaceutical companies. In addition to the halogens, the hydroxyl group and the methyl group have been attached to the steroid nucleus.

These modifications have afforded a new series of compounds which vary in anti-inflammatory effect and in their ability to influence retention of salt. The four best known of these compounds used in clinical medicine are prednisolone, methyl prednisolone, triamcinolone and dexamethasone. They are respectively △-1-hydrocortisone, 6α-methyl prednisolone, 16α-hydroxy-9α-fluoro-△1-hydrocortisone and 16α-methyl-9α-fluoro-△1-hydrocortisone. The last mentioned steroid is about thirty-three times more active than cortisone in terms of anti-inflammatory effects in man.

As in the investigation of epinephrine and thyroxine, progress in the study of the steroid nucleus has been step-wise. In 1950, no one could suggest what change in the structure of the hormone would dissociate the effect on mineral metabolism from the anti-inflammatory activity and no one could predict that the latter influence could be increased so much as thirty-three times.

Two results of change in the structure of the steroid nucleus can be predicted. The first is that addition of halogen at positions nine or twelve, that is, adjacent to position eleven, would increase the acidic property of the hydroxyl group which is attached at that point. This change in the chemical properties, suggested by Fried, well may be of importance.

The second result could be to make the compound more resistant to the enzymes which normally bring about inactivation of the cortical hormones. This would prolong the survival time of the molecule and hence its apparent activity. Whether these two suggestions are sufficient to account for the enhancement of activity of dexamethasone compared with cortisone has not been demonstrated.

Sarett has postulated that the structure of the material which reacts with hydrocortisone must be such that when the two are brought together, there will be a close fit. For this to be true, one side of the steroid molecule must be free of all groups except those which are engaged in the chemical reactions which are induced by the hormone. Inspection of the models of the many derivatives which have been made supports this hypothesis.

Research in clinical medicine has been given fresh stimulation by the availability of the new steroids. Dissociation of anti-inflammatory potency from retention of salt has broadened the scope of application and has removed one of the most serious side effects of the cortical hormones.

In a recent summary of the clinical investigations of steroid hormones and their derivatives, Bunim has pointed out that in addition to the three diseases first studied, that is, rheumatoid arthritis, rheumatic fever, and systemic lupus erythematous, quote "now included are certain diseases of the eye, skin, kidneys, lungs, heart, blood, blood vessels, gastrointestinal

tract, connective tissue and muscle. In general, the cortico-steroids have been found to be effective in suppressing reactions of inflammation and hypersensitivity."

Dr. Bunim's list is noteworthy and presents the most attractive part of the cavalcade of hormones and steroids. In fact, it is almost the end of the imposing parade. We can look forward to many more years which will be required to explore the use of cortisone as a tool for research.

In 1955, D. A. Long made the statement, "From the time of its discovery, it was obvious that cortisone, the therapeutic weapon, was of minor importance compared with cortisone, the tool with which to carry out fundamental and clinical research. Clinical evaluation of the drug is incomplete; the use of cortisone as a research tool has scarcely begun."

D. A. Long is one of the few investigators who have tried to find an explanation for the influence of cortisone in allergy. He approached the problem through a study of the effect of thyroxin, ascorbic acid and cortisone on the phenomenon of hypersensitivity, and observed that the first hormone increased and the latter two decreased sensitivity of the guinea pig to tuberculin.

The results seemed to be clear and not ambiguous. But after several more years of work he found that, for the guinea pig, the degree of hypersensitivity and the influence of the three hormones depended on the diet and also was linked intimately with the metabolism of carbohydrates. Furthermore, he showed that the effect of thyroxin was mediated through another hormone, insulin, and that the effect of ascorbic acid was closely related to the metabolism of the sulfhydryl group (the SH group) of glutathione and the fixed SH groups of tissues.

He concluded that the relative degrees of immunity and hypersensitivity in any one animal at a particular time are probably decided by the balance between the output of insulin and cortisone. This balance in turn is influenced by ascorbic acid and the other endocrine glands notably the thyroid.

The results of Long's work reveal some of the possibilities which are afforded by the use of cortisone as a tool for research. Whether the relationships which he has found in the guinea pig can be extended to the human being, I do not know.

I shall not prophesy about that possibility, but I am on firm ground when I point out that, regardless of new approaches to old problems, and new tools with which to work, future investigations must be planned and executed by human beings. Without doubt, there will be more lapses between the synthesis of new compounds and their utilization. There will be more pre-mature conclusions, more errors of judgment in chemistry, physiology, and medicine. But in spite of these delays, there will be steady and splendid progress in our understanding.

In closing, may I mention a warning to those who strive to enlarge our horizon in the field of physiology and medicine. Prof. Ralph Gerard

annually has pronounced this admonition to those impulsive workers in physiology who have not learned to be cautious and critical of their own work. It is this, "Young man, take care, lest you find what you're looking for."

From the vantage point of fifty years of research in biochemistry, may I add one more sentence. This is "Young man, take care, lest you stop before you've found what you're looking for."

3 Queenston Place

INTRAMUSCULAR OR INTRAVENOUS ANTIBIOTIC PREPARATIONS INTENDED FOR USE IN DAIRY ANIMALS: LABELING

During the past few years, the quantities of the various antibiotic preparations certified for use in the prevention and treatment of infections of dairy animals by the intramuscular and/or intravenous routes of administration have increased substantially. For example, the quantity of the combination drug penicillin and dihydrostreptomycin (dry and in suspension) certified for use in animals by injection has steadily increased since 1955. In that year, the batches certified contained a total of approximately 1.4 trillion units of penicillin and 2.7 million grams of dihydrostreptomycin. In 1956, 1957, 1958, and 1959, they contained approximately 3.8, 6.4, 13.9 and 34.2 trillion units of penicillin and 7.4, 9.2, 20.2 and 48.1 million grams of dihydrostreptomycin, respectively. Not only are more animals receiving antibiotics by injection, but substantially larger amounts of the drugs are administered per dose. Although the labeling for most of the penicillin-containing drugs recommends for injections of large animals a daily dose of from 2,000 units to 4,000 units per pound of body weight of the animal, doses up to five times the lower recommended dose are commonly used.

When a dairy animal is injected with sufficient quantities of an antibiotic preparation, detectable amounts of the drug are excreted through the animal's milk. The amount of drug excreted and the time of excretion depend upon the quantity of the drug administered per dose and the number of doses, as well as on the kind of preparation injected. Thus, the practice of injecting dairy animals with antibiotic preparations may result in the presence of these drugs in the milk supply unless the milk from treated animals is discarded for an appropriate time. Although the length of time that each antibiotic will persist in the milk of dairy animals treated with various dosages and kinds of antibiotic preparations by injections has not been definitely determined, from the Administration's experience with this class of drug, residues of some drugs persist for days after the latest injection. Therefore, in the interest of the public health, this potential portal of entry for antibiotics in the milk supply must be closed, and to do so users of these drugs must be informed through appropriate labeling. Therefore, the Commissioner proposes to amend the regulations for the certification of antibiotic and antibiotic-containing drugs (21 CFR Part 146) by adding thereto the following new section:

> 146.14 Antibiotic and antibiotic-containing drugs intended for use in the prevention or treatment of infections of veterinary animals by the intramuscular or intravenous route; labeling.

Whenever the label of an antibiotic drug included in the regulations in this chapter suggests or recommends its use in the prevention or treatment of infections of veterinary animals by the intramuscular or intravenous route of administration, the label of such drugs shall bear either the statement—"Warning: Not for use in dairy animals since this use will result in contamination of the milk with the antibiotic" or the statement—"Warning: Milk from treated dairy animals within ____ hours after the latest injection must not be used for human consumption," and the blank has been filled in with that figure which shall not be greater than 96, which the Commissioner has authorized the manufacturer of the drug to use. The Commissioner shall determine what such figure shall be from information submitted by the manufacturer which the Commissioner considers is adequate to prove that time after the latest injection that the milk from treated animals will contain no residues of the antibiotic.—From the *Federal Register*, April 9, 1960. GEORGE P. LARRICK, *Commissioner, Department of Health, Education and Welfare, Food and Drug Administration.*

EPISTAXIS IN ALLERGIC CHILDREN

ROLAND B. SCOTT, M.D., and ROSELYN PAYNE EPPS, M.D.
Washington, D. C.

DURING the past several years, it has been observed by one of us (RBS) that children with allergic conditions involving the upper respiratory tract appeared to suffer from nosebleeds more frequently than non-allergic children. When we consulted the leading American textbooks on Pediatrics, no mention was made of any etiological association or relationship between recurrent nosebleeds and allergic disorders involving the upper respiratory tract. Therefore, a study was undertaken (1) to determine the incidence of epistaxis in normal and allergic children, (2) to analyze the available data of fifty children in office practice observed to have epistaxis and allergy, and (3) to collect and summarize the observations of pediatric allergists regarding the relationship of nosebleeds and respiratory tract allergy.

METHOD OF STUDY

A clinical survey was made of 450 children selected at large from patients seen in private office practice and in the outpatient division of a general hospital. Information was obtained from the parents regarding the age, sex, frequency of nosebleeds, the apparent cause, seasonal incidence, the presence of allergy in the child and the history of allergy in the family. The children were placed into three groups on the basis of their allergic history: 1. Children with no overt allergic manifestation and no family history of allergy were classified as "normal"; 2. Children who had exhibited allergic manifestations were classified as "allergic"; 3. Children who had no overt allergies but had a family history of allergy (parents, siblings or grandparents once removed) were classified as "potentially allergic."

A more detailed analysis was made of another group of fifty patients from private office practice who were observed to have epistaxis and allergy. Additional information was extracted from their records such as age at onset of epistaxis and of allergy, hematology, appearance of nasal mucosa, cytological study of nasal secretions, intradermal skin test results, desensitization and therapy. Inasmuch as this part of the study was retrospective, complete information was not available on all of the patients.

In order to survey the experience of other observers, a questionnaire

From the Department of Pediatrics, Howard University College of Medicine and the Pediatric Services of Freedmen's Hospital and the District of Columbia General Hospital, Washington, D. C.

Dr. Scott is chief pediatrician at Freedmen's Hospital.

was sent to pediatric allergists throughout the country. Answers to the following questions were requested:

1. Have you observed an association of recurrent epistaxis in children with allergic rhinitis?

2. Would you expect children with allergic rhinitis, allergic sinusitis or allergic bronchitis to experience a greater incidence of nosebleeds than non-allergic children?

TABLE I. COMPARISON OF INCIDENCE OF EPISTAXIS IN ALLERGIC, POTENTIALLY ALLERGIC, AND NORMAL CHILDREN

Category	Total Cases	Cases With Epistaxis	Per Cent With Epistaxis
Frankly allergic	183	48	26.22%
Potentially allergic	78	19	24.35%
Normal	189	35	18.51%
Grand total	450		

	Difference In Incidence of Epistaxis	Significance* of This Difference	
Frankly allergic	7.71%	$p<0.03$	Normal
Potentially allergic	5.84%	$p<0.07$	Normal
Frankly allergic	1.87%	$p<0.19$	Potentially allergic
Frankly and potentially allergic	7.16%	$p<0.04$	Normal

*These p values taken from Table of Fractional Areas Under the Normal Curve.

TABLE II. DISTRIBUTION OF DIAGNOSES IN THE SIXTY-FOUR CHILDREN WITH EPISTAXIS WHO PRESENTED SINGLE ALLERGIC MANIFESTATIONS

Perennial allergic rhinitis	19
Bronchial asthma	19
Allergic dermatitis (eczema)	13
Pollinosis	6
Papular urticaria	3
Angioedema	1
Allergic bronchitis	1
Urticaria (hives)	1
Vernal catarrh	1
Total	64

3. With what type of allergies have nosebleeds been most frequently associated (pollinosis, perennial allergic rhinitis, bronchial asthma, atopic dermatitis, other)? Comments were also requested. Forty-nine of the fifty-seven pediatric allergists who were consulted returned their questionnaires.

RESULTS

We found approximately 8 per cent more nosebleeds in allergic than in normal children, and about 6 per cent more in the potentially allergic subjects (Table I). Both differences are fairly significant because they would be expected to occur by chance alone one in thirty-three and one in

TABLE III. DOUBLE ENTRY TABLE SHOWING CLINICAL MANIFESTATIONS IN TWENTY-THREE PATIENTS WITH TWO ALLERGIC CONDITIONS

	Bronchial Asthma	Perennial Allergic Rhinitis	Seasonal Allergic Rhinitis (Pollinosis)	Eczema	Angioedema	Allergic Bronchitis	Papular Urticaria	Urticaria	Vernal Catarrh	Drug Allergy
Bronchial Asthma		**	**	**						
Perennial Allergic Rhinitis	**		*	******						
Seasonal Allergic Rhinitis (Pollinosis)	**	*		*			**	*	*	*
Eczema	**	******	*	*		*	*			
Angioedema							*			
Allergic Bronchitis				*						
Papular Urticaria			**	*	*					
Urticaria			*							
Vernal Catarrh			*							
Drug Allergy			*							

TABLE IV. DISTRIBUTION OF DIAGNOSES IN THE NINE CHILDREN WITH EPISTAXIS WHO PRESENTED THREE ALLERGIC MANIFESTATIONS

1. BA, PAR, eczema
2. BA, PAR, vernal catarrh
3. BA, vernal catarrh, drug allergy
4. and 5. BA, eczema, pollinosis
6. Pollinosis, eczema, urticaria
7. Pollinosis, PAR, eczema
8. PAR, allergic bronchitis, papular urticaria
9. PAR, eczema, allergic bronchitis

Code: BA=bronchial asthma
PAR=perennial allergic rhinitis.

fourteen, respectively. There was no significant difference in the incidence of epistaxis in the allergic and potentially-allergic groups. Finally, there were about 7 per cent more allergic and potentially-allergic children than normal children with epistaxis. This difference is significant and has a chance expectancy of about one in twenty-five. These results strongly suggest that allergy either present or potential may predispose to epistaxis. This conclusion is supported by a little better than the 5 per cent level of confidence.

There was no significant difference in the incidence of epistaxis in the sexes. (Of forty-eight allergic children with epistaxis, 48 per cent were females and 52 per cent were males.) There were 275 male and 225 female children in the entire study. The age distribution was as follows: infants less than two years of age, 112; preschool children aged two to five years, 138; children five years or older, 200.

Of the ninety-eight children with epistaxis who showed overt allergic conditions (forty-eight patients from the clinics and fifty from private

practice), sixty-four had single allergic manifestations (Table II), twenty-three presented two allergic disorders (Table III), nine had three allergies (Tables IV) and two exhibited four allergic syndromes.

The apparent trigger mechanisms of epistaxis are listed in Table V.

TABLE V. PRECIPITATING CAUSES OF EPISTAXIS IN FIFTY-NINE ALLERGIC PATIENTS

	Number	Per Cent
Upper respiratory infection	15	25.42
Physical trauma (picking, rubbing, etc.)	13	22.03
"No apparent cause"	13	22.03
Sneezing	11	18.64
Exercise or excitement	5	8.47
Cough	2	3.38
Total	59	99.97
No report of cause	39	

Prominent excitatory agents were upper respiratory tract infections, physical trauma and sneezing. In one-fourth of the cases there was no apparent precipitating agent.

TABLE VI. INTRADERMAL SKIN TEST RESULTS IN FORTY-FOUR ALLERGIC PATIENTS WITH EPISTAXIS

	Number Reacting	Per Cent
Dust	44	100
Ragweed	23	52.27
Feathers	22	50.0
Alternaria	15	34.09
Cat epithelium	13	29.54
Dog epithelium	12	27.27
Grasses	11	25.0
Plantain	10	22.72
Horse epithelium	9	20.45
Pyrethrum	8	18.18
Trees	7	15.9
Gum arabic	7	15.9
Timothy	6	13.63
Kapok seed	5	11.36
Horse serum	5	11.36
Cotton seed	4	9.09
Karaya gum	4	9.09
Hormodendrum	2	4.54
Rabbit epithelium	1	2.27
Wool	1	2.27

The records of fifty-four allergic children with epistaxis contained sufficient information to determine the seasonal incidence of bleeding. The results were as follows:

Winter only .....22.2 per cent of cases
Spring only .....14.8 per cent of cases
Summer only .....14.8 per cent of cases
Fall only ..... 5.6 per cent of cases
Perennial .....42.6 per cent of cases

Of nineteen allergic patients who had blood differential smears, twelve showed eosinophil counts within the normal range, and seven were elevated.

Of twenty-three children, the hemoglobin value was less than 10 gms in six and more than 10 gms in seventeen children. There was no relationship between the hemoglobin level and the percentage of eosinophils in nineteen children when the two were plotted in a full scatter graph.

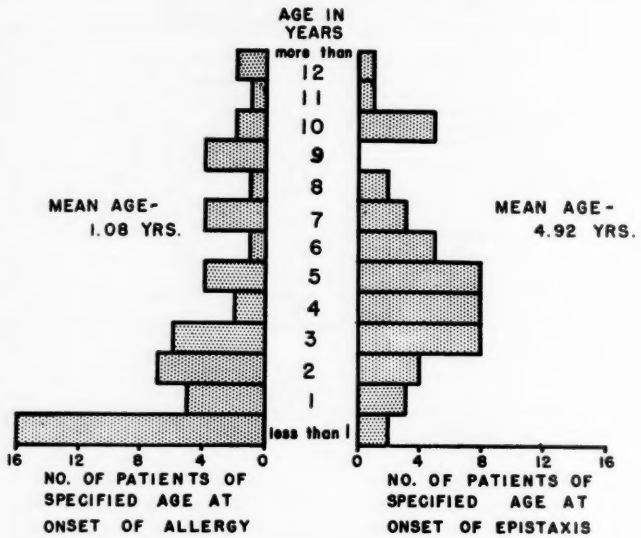

Fig. 1. Comparison between ages of onset of clinical allergy and epistaxis in fifty patients.

Thirty-seven of forty patients exhibited the typical pale, boggy allergic appearance of the nasal mucous membrane. In three patients, the nasal mucous was described as crusted or excoriated.

The results of intradermal skin tests performed on forty-four patients revealed a significant incidence of positive reactions to house dust, feathers, animal dander and pollen (Table VI).

A comparison was made between ages of onset of allergy and epistaxis in fifty patients. In general, the allergic manifestations appeared before the onset of epistaxis (Fig. 1). The mean age of onset of allergy was 1.08 years and the mean age of onset of epistaxis was 4.92 years.

In response to the question, "Have you observed an association of recurrent epistaxis in children with allergic rhinitis?", 71.5 per cent of the pediatric allergists who replied answered "yes," 26.5 per cent stated "no" and 2 per cent left the question unanswered.

In response to the question, "Would you expect children with allergic rhinitis, allergic sinusitis or allergic bronchitis to experience a greater incidence of nosebleeds than normal children?", 75.5 per cent of the physicians who replied answered "yes" and 16.3 per cent answered "no."

The remainder (8.2 per cent) either left the question unanswered or gave an equivocal reply.

In response to the question, "With what types of allergies have nosebleeds been most frequently associated?", forty-four replies were received with the following results:

Perennial allergic rhinitis	32
Pollinosis	20
Not observed	4
Other: vasomotor rhinitis	1
Bronchial asthma	0
Atopic dermatitis	0

In addition to categorical answers, the physicians were invited to make comments regarding the first two questions. In answer to the question, "Have you observed an association of recurrent epistaxis in children with allergic rhinitis?" comment varied from a laconic "yes" or "no" to some of the following:

"I believe allergic rhinitis to be the most common cause of nosebleeds in children."

"The presence of nosebleeds in a child with a family history of allergy almost makes the diagnosis of allergic rhinitis."

"Yes, many times this is their first symptom."

Most of the allergists who answered the question by a "No" did not bother to make further comment. An exception was one physician who replied, "I have only had two such cases in all the children that I have treated."

In answer to the second question, "Would you expect children with allergic rhinitis, allergic sinusitis or allergic bronchitis to experience a greater incidence of nosebleeds than non-allergic children?", most of the physicians who commented beyond a "yes" or "no" were those who answered in the affirmative. The comments in general dealt largely with the mechanism of bleeding such as "mechanical irritation from itching and rubbing," "mucous membrane of allergic children more susceptible to infection and injury," "chronic congestion predisposes the nasal mucosa to bleeding."

DISCUSSION

This study indicates a significant association between nosebleeds and allergic manifestations, particularly those involving the respiratory tract in children. The mechanism of local bleeding may be attributed to both intrinsic and secondary factors. In regard to the former, we may cite the characteristic local edema of the nasal mucosa as the earliest and most common expression of increased capillary permeability in allergic disorders involving the nose, bronchi, etc. More severe capillary damage may find expression as diapedesis (epistaxis).[1] The plexus of vessels found in the lower anterior part of the nasal septum (Kisselbach's area) appears to be particularly vulnerable to hemorrhages.[2]

Such hemorrhagic manifestations as purpura (simple and thrombocytopenic), hematuria, melena, menorrhagia, et cetera, have been described by many authors as being allergic in origin.[3] Among the reported causative allergens are such foods as milk, potato, wheat as well as sera, inhalants and drugs (quinine, ergot, sedormid, estrogens, et cetera). The reactions are often of the delayed type, so that nosebleed may appear spontaneously at night during sleep. This may account in part for the relatively large number of cases where the parent could attribute no apparent cause for the onset of the bleeding episode.

Rapaport has observed that capillary fragility was increased in 49 per cent of allergic children and in 23.6 per cent of normal children.[4] Cohen and Vaughan similarly noted the increased frequency with which allergic patients bruised.[3] Scal has called attention to the susceptibility of allergic individuals with vasomotor rhinitis, hay fever and sinusitis to nosebleeding as a result of increased capillary fragility and permeability.[5]

In addition to the fundamental factors mentioned above, secondary conditions such as superimposed infection, mechanical irritation from rubbing, picking and hard blowing of the nose undoubtedly may aggravate or precipitate epistaxis. The intractable nocturnal cough often associated with the post-nasal drip of allergic origin and with the sino-bronchitis syndrome may be an additional factor in some cases.

Our chief interest in this communication is in emphasizing the importance of recurrent or periodic nosebleeds in children as a leading sign or a "red flag" indicative of a possible underlying and often unrecognized state of allergy involving the upper respiratory tract (especially when the mucous membranes of the nose and accessary sinuses are involved as the shock organs). Horesh[6] and Glaser[7] have mentioned epistaxis as a clinical manifestation of respiratory tract allergy.

A diagnosis can best be established by combining information derived from the history, physical examination, skin testing and cytological examination of nasal secretions. The importance of visual inspection of the nose is illustrated by the finding of a typical pale, edematous, boggy, nasal mucosa in 90 per cent of the recorded cases in this study. House dust, feathers, dog and cat dander, mold and pollen were the inhalants most frequently associated with epistaxis in allergic children in this study. Many of the children had skin tests to foods, but they were not routinely performed and are not included in the analysis.

A preponderance of eosinophils in the nasal smear is helpful and confirmatory of an allergic rhinitis. Unfortunately, the status of the cellular response in any one patient is not static but may vary considerably from one examination to the next. In emphasizing the importance of a study of nasal cytology, Hansel states that a pure eosinophilic response in the nasal secretions is indicative of the occurrence of an allergic reaction in the local tissues and that complicating infections are characterized by a neutrophilic response.[8] Cooke, however, contends that although the

presence of a preponderance of eosinophils in the nasal smear is indicative of the allergic nature of the rhinitis, it does not distinguish non-infective (of inhalant or food origin) from infective allergic rhinitis (bacterial allergy) because eosinophilia may be found in both types.[9]

Roentgenograms of the accessary nasal sinuses are indicated in selected cases of long standing or refractory nature. If mouth breathing persists even after shrinkage of the nasal mucous membrane, a lateral roentgenogram of the nasopharynx often reveals hypertrophied adenoid tissue. If there is an associated protracted nocturnal cough, x-ray films of the chest and paranasal sinuses may aid in diagnosis of the sino-bronchitis syndrome.

In the differential diagnosis of nosebleeds in children, one has to keep in mind, of course, the possibility of certain systemic diseases such as rheumatic fever, nephritis, typhoid fever and primary blood dyscrasias as well as local conditions (such as hemangiomas, hereditary telangiectasis or a foreign body in the nose). In the fifty children with epistaxis observed in consultative practice in this study, the presence of allergy involving the upper respiratory tract was the only obvious primary causative factor.

In a study of thirty-four children with epistaxis who were referred for hematologic work-up, Schulman[10] was able to divide the cases into two distinct groups on the basis of history and physical examination. In the first category (seventeen cases), epistaxis was the only indication of an abnormal tendency to bleed. When subjected to a complete hematologic investigation, no child in this group was found to have any coagulation abnormality. Characteristically, the nosebleeds often occurred at night without evidence of antecedent trauma. In some children, the bleeding appeared to be precipitated by physical exertion and exposure to very hot weather. The pathogenesis was obscure but was attributed to the possibility of local pressure changes within the nasal cavity.

By contrast in Schulman's second group of seventeen children, there was a history of an abnormal tendency to bleed (easy bruising, persistent oozing from sockets after dental extractions and following tonsillectomy). Moreover, there was frequently a history of other members of the family who were known to bleed excessively. Laboratory studies disclosed a hemorrhagic disorder in sixteen of the seventeen children in this category.

MANAGEMENT

The management of epistaxis caused by allergic rhinitis or associated allergic conditions can best be achieved by the standard methods of detecting the causative allergens followed by their elimination and/or hyposensitization. In our experience, the individual hemorrhagic episodes were not extensive and usually ceased spontaneously or were controlled by simple home measures, even though they tended to recur. Unless the causative allergen is detected and treated, local cauterization alone is not likely to give lasting benefit. Frequently recurring nosebleeds may lead to

an iron deficiency anemia which may require the administration of a hematinic. During the early course of an allergy survey, we have employed symptomatic medication in the form of ascorbic acid 100 mgm given three times a day and antihistamines orally for the relief of nasal

TABLE VII. CLINICAL MANIFESTATIONS OF NASAL OR PARANASAL ALLERGY

1.	Stuffy blocked nose
2.	Mouth breathing
3.	Enlarged adenoid mass
4.	Allergic salute
5.	Transverse groove on bridge of nose
6.	Soft flabby nose which has been excessively massaged from rubbing
7.	Pale boggy mucous membrane
8.	Thin watery nasal secretion
9.	Eosinophilia in nasal smear
10.	Thickened membranes (opacification of sinuses) by x-ray examination
11.	Cough of sino-bronchitis
12.	Post-nasal drip
13.	Rashes and excoriations about nostrils and upper lip
14.	Recurrent nosebleeds

edema. In general we avoid the use of nose drops. As a rule, symptomatic medication can be decreased or omitted entirely after the institution of specific allergy treatment.

SUMMARY

Children who present recurrent epistaxis as a complaint should be carefully examined for evidence of allergy, particularly involving the upper respiratory tract. The presence of this symptom should serve as a "red flag" to induce the physician to employ well established procedures for the detection of an underlying allergic rhinitis or allergic sinusitis. The omission of this symptom as a sign of nasal allergy in the leading American textbooks on pediatrics indicates that its diagnostic significance in relationship to allergy in childhood is not generally appreciated at the present time by practitioners at large.* We desire to add the symptom of epistaxis to the list of well established clinical manifestations of nasal or paranasal allergy in childhood (Table VII).

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Department of Pediatrics (Dr. Scott)
Freedmen's Hospital
6th and Bryant Streets, North West

NEW PROGRAM REGARDING NEW DRUGS

A program for the reporting of unusual or adverse reactions to drugs was announced recently by the Food and Drug Administration. It will be conducted initially with a limited number of hospitals selected to represent a cross section of medical specialties. Where necessary, contracts may be negotiated with the hospitals (or individual physicians designated by them) providing for reimbursement. As the program develops, it is planned that additional hospitals will be included with the aim of establishing nation-wide reporting. The project is an outgrowth of a voluntary pilot study carried out during the past four years in cooperation with the American Association of Medical Record Librarians, the American Society of Hospital Pharmacists, the American Medical Association, and the American Hospital Association.

The program is designed to develop information promptly on the untoward effects of drugs, especially the newer drugs. The information will be utilized by FDA in the resolution of medical and administrative problems under the Federal Food, Drug, and Cosmetic Act.

Prior to release for general use, new drugs are required to be evaluated from the standpoint of safety by the Bureau of Medicine of the Food and Drug Administration. Notwithstanding a most careful check of the submitted data, wide clinical use may bring to light effects not apparent in the investigative studies. When these become known, appropriate measures are taken to afford a greater degree of patient protection. Remedial steps necessary on the part of the drug manufacturer or distributor may vary from a change in the labeling, alerting physicians and others responsible for patient care, to a complete removal of the drug from the market.

The Food and Drug Administration has previously had to rely on the published literature and sporadic reports from physicians, institutions and pharmaceutical manufacturers to supplement its own small staff in following up on experience with new drugs.—U. S. Department of Health, Education and Welfare, Food and Drug Administration.

TYPES OF SENSITIZATION DISCLOSED BY POSITIVE PATCH TESTS TO PARAPHENYLENEDIAMINE AND BENZOCAINE

L. EDWARD GAUL, M.D.

Evansville, Indiana

AMONG 580 dermatologic patients, there occurred fifty positive patch tests to paraphenylenediamine (PPD) (9 per cent), and sixteen to benzocaine (3 per cent). Only seven of the tests, and these were limited to PPD, were graded 1 to 2 plus. These chemicals can be considered strong elicitors. The sex distribution was twenty male and thirty female patients for PPD, and six male and ten female patients for benzocaine. Ordinarily, a positive patch test is considered evidence for a contactant allergen. This concept was doubted especially as it referred to PPD. Efforts to find a responsible dye were frequently unsuccessful.

All patients had had screening patch tests with the following test substances: potassium chromate 1 per cent aqueous, nickel sulfate 1 per cent aqueous, mercuric chloride 0.1 per cent aqueous, formaldehyde 1 per cent aqueous, monobenzyl ether of hydoquinone 1 per cent petrolatum, mercapto benzothiazole 1 per cent petrolatum, tetramethylthiuram monosulfide 1 per cent petrolatum, PPD 2 per cent petrolatum, benzocaine 1 per cent petrolatum, rhus resin 0.1 per cent petrolatum and thiosalicyclic acid 0.1 per cent petrolatum. As indications arose, the list was increased to include clothing materials, footgear, hair dyes, food colorings, topical drugs, cosmetics, soaps and detergents. Four patients were excluded because of incomplete records, leaving a total of forty-six for this study.

Types of sensitization disclosed by PPD and benzocaine patch tests were studied by correlating the degree and duration of positive response with the presenting dermatitis. The circumstances attending each attack were weighed in light of patch test results. Drug reactions were catalogued in relation to their station in the dermatologic background. The events from histories had to complete the clinical picture rather than be accepted unreservedly. Multiple and delayed patch tests were reviewed in relation to the onset, persistence and involution of the dermatitis.

TYPES OF SENSITIZATION DISCLOSED BY POSITIVE PPD TESTS

Two important features characterize a positive PPD test; it is one of the most common causes of reaction, and it is one of the most informative. The clinical information to be obtained will be described below and summarized in Table I. A major obstacle was the inability to obtain precise information on the kinds of drugs administered.

I. Non-specific Sensitivity (1 to 2 plus patch test reactions).—These PPD tests appeared as erythema with or without a slight edema. Itching

TABLE I. CORRELATION OF POSITIVE PPD AND BENZOCAINE PATCH TESTS WITH TYPES OF SENSITIZATION

Types of Sensitization	Positive Patch Tests			
	PPD Alone	PPD and Benzocaine	Benzocaine Alone	Per Cent
I. Non-specific sensitivity (1 to 2 plus patch tests)	7			15
II. Drug reactions (vascular sensitivity) (3 to 4 plus patch tests)				45
1. Procaine	3	3		
2. Penicillin	4	3	2	
3. Sulfonamide	3	3	1	
4. Procaine, penicillin and sulfonamide		2		
a. Cross-sensitivity*		(3)		
b. Cross and multiple sensitivity**		(1)		
c. Multiple without cross-sensitivity†	1	(4)		
III. Multiple sensitivities‡ (eczematous sensitivity)	13	1		30
IV. Delayed reactions	4			10
Total	35	12	3	

* Immunochemical relationship between primary and secondary allergens.
** Immunochemically related and immunochemically unrelated allergens.
† No immunochemical relationship.
‡ Primary sensitization to immunochemical unrelated allergens.

was trivial or absent. A critical feature was the short duration of a day or two. One reaction lasted four days.

Seven patients were seen, two female and five male. The clinical diagnoses were erythema multiforme, hand eczema three, infectious eczematoid dermatitis, pustular psoriasis and dyshidrotic eczema.

II. Drug Reactions (3 to 4 plus patch test reactions).—These PPD tests were characterized by erythema, induration, persistence and pruritus. Some lasted a month or six weeks, a few even longer. A button-like induration was almost diagnostic.

1. *Procaine.*—These cases are uncommon, a total of six; two male and four female over three years. They present swelling, redness, tenderness and pain at the site of injection. The onset is rapid, a few hours with symptoms and signs present a week, more or less. Two patients were followed. They developed no systemic manifestations except malaise and discomfort. Every drug reaction of this type from procaine has been associated with a positive PPD test. There have been many instances of patients declaring that procaine made them feel "flighty, nervous, faint or nauseated" with negative PPD tests. Procaine is the usual local anesthetic in this region, but it was impossible to be sure that it was used in every patient.

In two patients there was evidence that a positive PPD test revealed a specific vascular sensitivity to procaine. Penicillin and sulfonamides were tolerated. In Case 1 there was also present a vascular sensitivity to salicylates. In Case 4 a dermatitis preceded the procaine reaction. In Case 5 a merthiolate and benzocaine sensitivity was established by patch test before the procaine reaction. In Case 6 the procaine reaction preceded the dermatitis. In Cases 4, 5, and 6 penicillin and sulfonamides were tolerated,

again pointing to specificity for the procaine reaction, and these cases also showed concurrent sensitivity to benzocaine.

2. *Penicillin.*—There was a total of seven patients, four male and three female. In four patients, the kind of penicillin administered was unknown. None of the penicillin reactions were observed personally. The history of a penicillin reaction, while perhaps being an indication for a PPD test, should not be considered an assurance that a positive test will occur. Further evaluation is needed.

In Cases 1, 2, 3, and 4 there was evidence that the vascular sensitivity to penicillin was specific. Procaine and sulfonamides were tolerated. Cases 5, 6 and 7 had an associated sensitivity to benzocaine. They, too, had had procaine and sulfonamides without reaction. Four cases had dermatitic involvement preceding the drug reaction, and three cases recorded the onset as due to the drug reaction. It may be significant that a reaction at the injection site from procaine penicillin was recalled by three of the patients.

3. *Sulfonamides.*—There was a total of six patients, one male and five female. An authentic history of a sulfonamide drug reaction, or a dermatitis from topical use, is quite apt to be associated with a positive PPD test. The history in these patients was a little different. Each one dated the onset of dermatitis with the sulfonamide reaction. In four patients it heralded numerous attacks and chronic dermatitis. Three patients were tolerant to procaine and penicillin indicating specificity for the antigen. The patient represented by Case 2 might have been intolerant to penicillin and, in addition, procaine used to obtain a biopsy specimen caused a slough. The patient of Case 3 was seen with a sulfonamide dermatitis. A negative patch test to the drug and a positive test to PPD points to a metabolite of the sulfonamide being the antigen for PPD.

4. *Procaine, Penicillin and Sulfonamides.*—Two patients, one male, and one female, were members of this group. They were described as Cases 5 and 6 in a previous report,[1] and support the interpretation that each drug reaction produces a specific antigen for the respective drug; or the antigen formed by one drug reaction becomes receptive to alteration by other drug reactions, so that regardless of which one is administered, an immediate reaction occurs. The high attack rate of dermatitis in these cases points not only to cross-reactiveness, but also to a disposition to multiple eczematous sensitizations. Drug reactions designated as "vascular sensitivity" seem to prepare the skin for three distinct varieties of eczematous sensitization [Table I, Drug Reactions, (a), (b), (c)].

(a) Cross-sensitization (immunochemical relationship between primary and secondary allergens).—Significance is attached to the finding of benzo-

caine sensitivity in about half the patients. In two patients there was a proven benzocaine sensitivity before the vascular sensitivity; in four patients there had been previous attacks of dermatitis (possible "caine" sensitivity); and in three patients there had been no previous dermatitis. Two explanations are advanced: 1. A pre-existing "caine" eczematous dermatitis might have been present and influenced the onset of vascular sensitization. 2. The procaine, penicillin and sulfonamide drug reaction might have supplied an additional and specific antigen for benzocaine. Case 6 (sulfonamide reaction) was considered a proven instance of cross-sensitivity and, in addition, other cases with concurrent benzocaine sensitivity were suspected. These comments would be incomplete if reference were not made to the findings of Fisher and Sturm.[4] Twenty patients with eczematous sensitivity to procaine were retested. Two out of twenty developed an eczematous reaction at the site of intracutaneous procaine, and two developed a pruritic, tender nodule at the site of subcutaneous injections of procaine. These reactions did not occur in twenty controls. It would appear that the status of eczematous sensitivity must be studied thoroughly when cross-sensitivity is interpreted.

(b) Cross and multiple sensitivity.—This variety can occur in the presence of cross-sensitivity where patch test reactions are found to allergens immunochemically unrelated to the cross-sensitizing allergen. Case 4 (penicillin reaction) was sensitive to nickel, yet also showed cross-sensitivity to 2,4 toluenediamine.

(c) Multiple without cross-sensitivity.—A drug reaction or vascular sensitivity raises the threshold or enhances the predisposition to eczematous sensitivity independent of any immunochemical relationship. Case 5 (procaine reaction) showed positive patch tests to monobenzyl ether of hydroquinone and thiosalicylic acid; Cases 1 and 5 (penicillin reaction), formalin and chromate; and Case 1 (sulfonamide reaction), mercury and formalin. Quite commonly, patch test reactions have been seen to the above chemicals in the presence of negative tests to PPD and benzocaine.

III. Multiple Sensitivities (Eczematous Only), Primary sensitization to immunochemical unrelated allergens.—A remarkable feature of these fourteen patients was their complete refractoriness to drug reactions. All of them tolerated procaine several to many times. All but one had had sulfonamides. All but three had had penicillin, and two mentioned having had over 100 injections. The absence of susceptibility to drug reactions did not influence the development of epidermal or eczematous sensitization. In fact, the disposition to develop one sensitivity apparently opened the door for more. Immunologically, almost finicky specificity was found. Seven patients had a positive history of dermatitis from dyes (Table II). This was confirmed in Case 12. The

TABLE II. MULTIPLE SENSITIVITIES IN PPD SENSITIVITY

Case	Sex	Age	Other Patch Test Positivities and Order of Reactivity	Remarks
1	M	54	None	Dermatitis legs and arms from blue pants, red shirt
2	M	49	Merthiolate, tetramethyl thiuram monosulfide, formalin, nickel, mercury	Recurrent dermatitis for eight years, red shirt
3	M	39	Procaine	Hand dermatitis recurrent for six years
4	M	60	Rhus, monobenzyl ether hydroquinone	Cheilitis eight years, two attacks of poison ivy
5	M	55	Merthiolate, benzocaine	Three attacks of dermatitis
6	M	65	Chromate	Hand eczema, many years, blue gloves
7	M	64	Resin nail coating (brown)	Two attacks hand dermatitis
8	F	46	Nickel, tetramethyl thiuram monosulfide	Rash from egg dye, four attacks of dermatitis
9	F	63	Formalin	Axillary dermatitis, recurrent six years, blue dress
10	F	40	Chromate, mercaptobenzothiazol	Shoe dermatitis, six months
11	F	20	Rhus	Two attacks of rhus, rash from blue denim
12	F	46	Blue dress, blue hose, elastic	Recurrent dermatitis ears, neck, groin, legs and hands, seven years
13	F	21	Mercury, formalin	Hand dermatitis, two attacks
14	F	60	Surfacaine	Flexural eczema, recurrent many years; red food coloring caused itching?

positive PPD test indicated only eczematous sensitization. The test itself tended to be less reactive than the other positivities. It was the same grossly, as in the drug groups. The histology was not attempted.

One patient showed benzocaine sensitivity, but this was offset by thirteen who did not. These findings help to exclude any cross-reactiveness between PPD and benzocaine in eczematous sensitization. To include other reactors in the Table as instances of cross-reactions is discouraged by finding in the entire series (580 patients), numerous positive tests to these substances in the presence of negative PPD tests. A surprise occurred in Case 4, a dentist. Procaine induced a vesicular patch test reaction, yet benzocaine was non-reactive which is more evidence for specificity in eczematous sensitivity. Case 15 had applied surfacaine to an irritation on the left forearm. Eight days later—time for sensitization—a weeping dermatitis developed followed by immediate spreading to the right arm, face and neck. This emphasizes the ease with which strong sensitizers can induce dermatitis in the presence of eczematous sensitizations.[2]

IV. Delayed Reactions.—Approximately one out of ten reactions to PPD is delayed. Four cases were noted with delays of five days, ten days, two weeks and four weeks, respectively. Procaine had caused no reaction in these patients. While PPD test was still positive, dental procaine was used in one without any local reaction and without any effect on the PPD test. This patient also showed multiple sensitivities to nickel and chromate. Another patient was sensitive to formaline. Two patients had had sulfonamide without reaction. Two had had penicillin without reaction.

The case reported in,[1] whose PPD test was delayed two weeks was seen

in April, 1959, for a flexural dermatitis of three months' duration. In 1954, a chronic dermatitis of the feet and legs was present which persisted for many months. Penicillin was thought to be responsible for a "swelling" of the feet. Dental procaine was tolerated, also sulfonamides. There was an associated sensitivity to 4-4 dimethoxy diphenylamine. The flexural dermatitis had been well seven months. About this time, a triple sulfonamide (sulfadiazine, sulfamerazine, and sulfamethazine) was taken for a cold, also a cold tablet (aspirin, phenacetin, and caffeine) in full dosage for four days without any reaction. Three weeks after this period of medication, a second PPD patch test was done. Itching necessitated removing the patch in thirty-six hours. When read in forty-eight hours, there was present a papular eczematization about 3 centimeters in diameter. This experience supports a comment by Fisher[3] that delayed patch test reactions may well be the primary induction of sensitization. Other positive reactions in this group were not delayed.

V. Benzocaine Sensitivity Alone.—In the entire group of 580 patients patch tested, there occurred four cases of benzocaine sensitivity independent from PPD sensitivity. There was adequate opportunity for them to react simultaneously because they were placed side by side on the testing patch. The occurrence of independent benzocaine sensitivity is additional evidence for the absence of any cross-reactivity between these two allergens in eczematous sensitivity.

It is, perhaps, more than a coincidence that in three out of three histories, there was a record of drug reactions. Significant, too, is the fact that in the sixteen cases of benzocaine sensitivity, there was a drug reaction history in fifteen. This permits a doubt regarding the authenticity of the history in Case 5 of Table II. These cases support the contention that drug reactions from procaine, penicillin and sulfonamides can produce an antigen, specific for benzocaine and independent of that for PPD (explanation 2 under cross-sensitivity). These patients also displayed an ease to develop multiple eczematous sensitivities, and additional study may also reveal a tendency toward cross-reactiveness. In about one-fourth of the positive PPD tests, there should occur concurrent benzocaine sensitivity.

DISCUSSION

The types of sensitization outlined in Table I have become a convenient guide for classifying patch test results. They were reviewed in relation to the varieties described by Baer.[5] Type I would be placed in the category of Multiple Non-Specific Eczematous Sensitivity. "Here there is a heightened susceptibility to the primary irritant effect of many chemically and immunologically unrelated substances. These patients have a skin threshold for irritation so low that normally non-irritant concentrations exert a primary irritant action." PPD is prone to do this and also potassium chromate.[6] A second variety was Multiple Allergic Eczematous Sensi-

tivity—*secondary*, or cross-sensitizations.[5] This variety would come under Drug Reactions or Type II. The vascular sensitivity sets the stage for three classes of cutaneous manifestations or eczematizations; (a) cross-sensitivity, (b) cross and multiple sensitivity, and (c) multiple without cross-sensitivity. The third variety was Multiple Allergic Eczematous Sensitivities—*primary*. "These sensitizations are based upon a specific allergic mechanism, are produced by immunochemically unrelated allergens and occur in persons who have a greater than average susceptibility.[5]" It is believed that the "greater than average susceptibility" factor has one explanation. In Type II sensitization (class c), the vascular sensitivity raised the level of susceptibility. In Types III and IV sensitizations, these subjects appeared to have, for some unknown reason, a disposition to contactant eczematizations.

PPD was found to be one of the most common causes of patch test reactions by Fisher, Pelzig and Kanof.[7] During 1956, they found in 712 patients patch tested to PPD, that twenty-six (3.6 per cent) gave 3 or 4 plus reactions. In forty-five cases of PPD sensitivity, PPD reacted alone in twenty-eight, together with benzocaine in eleven, with procaine and benzocaine four, with p-aminobenzoic acid and benzocaine three and with sulfanilamide one. Meltzer and Baer[8] described a patient initially sensitive to benzocaine who later developed a reaction to oral sulfonamide and still later developed a dermatitis from a sunscreen. Patch tests were positive to monoglycerol p-aminobenzoate, procaine, butesin, PPD, aniline, sulfaguanidine, picric acid and azodye A.

Sidi and Dobkevitch-Morrill[9] found that in thirty cases of sulfonamide dermatitis (patch test positive), twenty of the patients showed 2 to 4 plus patch test reactions to PPD. In ten cases of dermatitis from local anesthetics (patch test positive), eight patients showed 2 to 4 plus patch test reactions to PPD. In fifteen cases with a PPD dermatitis, procaine ingestion caused a local reaction in one and a local and general reaction in another. An injection of procaine caused one patient to collapse with choking and angioneurotic edema. Sulzberger and Baer[10] in commenting on this case considered that it indicated the presence of a vascular, urticarial type sensitivity in addition to the eczematous type sensitivity. Reis, Gahwiler and Lustig[11] described four patients allergic to black hair dye, two of whom showed positive tests to procaine.

SUMMARY

A positive PPD patch test is commonly encountered and relays valuable clinical information. Approximately half of the 3 to 4 plus reactions were associated with a drug reaction to procaine, penicillin or sulfonamide. Cross-sensitization appears to be dependent upon a concurrent vascular sensitivity. Multiple sensitizations without vascular sensitivity tended to be highly specific. Approximately one-fourth of the 3 to 4 plus PPD tests were associated with a benzocaine sensitivity. In eczematous sensitization,

PPD and benzocaine are uncommon co-reactors; but in vascular sensitivity, cross-reactiveness should be looked for and investigated.

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509 Hulman Building

DANGERS OF PROLIFERATION OF PHARMACEUTICAL PRODUCTS

How many of us are using drugs that we haven't had time to stop and examine carefully? We can't remember what their chemical name is; we couldn't draw their configuration on the blackboard to save our necks; we have a great deal of trouble remembering the binominous system: the professional or trade name and the chemical name. The latter is often so very long that it takes more than a line of type. We trust implicitly, and think the Federal Pure Food and Drug people do too, the statements of at least the leading manufacturers, the so-called ethical producers, that they have properly screened these things for toxicity, but we are playing with fire. If we don't use them, we're guilty of being old fashioned and obstructive and of taking too long to catch up with current trends; if we do use them, we run the risks of late toxicity—the development of polyarteritis nodosa or other horrors yet undreamed of, because these things have been proliferating too rapidly, are being introduced too quickly and in too great profusion for the body of practicing physicians possibly to digest them in any proper sequence.—SEDGWICK MEAD, "Essay on the Art of the Practice of Medicine," *Kaiser Foundation Medical Bulletin*, 7:284 (Oct.-Dec.) 1959.

A COMPARISON OF SKIN TESTS BY IONTOPHORESIS, SCRATCH AND INTRADERMAL TECHNIQUES

SUSAN C. DEES, M.D., F.A.C.A., and JACK C. EVANS, M.D.
Durham, North Carolina

THE PRESENT report is a re-evaluation of the method of skin testing to allergens by iontophoresis. The introduction of allergens and other substances into the intact skin has been described by Abramson,[1] Dutton,[2] Morse,[3] Grosberg and Peshkin[4] during the past twenty-five years. Interest in this method centered about the pathways of penetration of the skin, the electrical charge of the skin, and the variety of substances which could be introduced into the skin by iontophoresis.[5] The movement of undissociated substances through the intact human skin was demonstrated by Dutton, Abramson and Peshkin. The predominant pathway was shown to be through the sweat glands. It was observed that skin trauma, discomfort, the time necessary for performing tests, and the number of positive results were all decreased by this technique. Since all of these features are of particular importance and are desirable in dealing with pediatric patients, it seemed again worthwhile to compare this method of skin testing with the scratch and intradermal techniques. In order to have some standard of references, we adhered as closely as possible to the iontophoresis techniques previously reported.

Materials and Method.—Electrical source to deliver at least 1.5 Milliamperes (Fig. 1).

1—Ammeter
1—Rheistat-switch
2—45 volt "B" batteries
1—5″ x 7″ wire mesh covered on one side with electrical tape
1—Flat zinc electrode 4″ x 6″
1—Carrying case
24—Gripper-snappers
Cotton, absorbent
Gauze
Allergens

By placing electrodes containing allergens on the back, and an electrode on the abdomen to complete the circuit, a flow of water is produced which carries the allergens into the sweat glands. In the present experiment as

From the Department of Pediatrics, The Duke University Medical Center, Durham, N. C.
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in those reported by Morse, the negative pole was used to transmit the allergen. A modification of the iontophoresis apparatus described by Morse was constructed by our electronics staff. This apparatus consists of a wire mesh electrode fitted with twenty-four gripper-snapper attachments

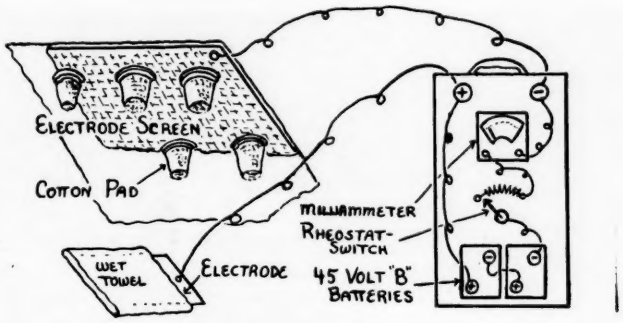

Fig. 1. Apparatus diagram.

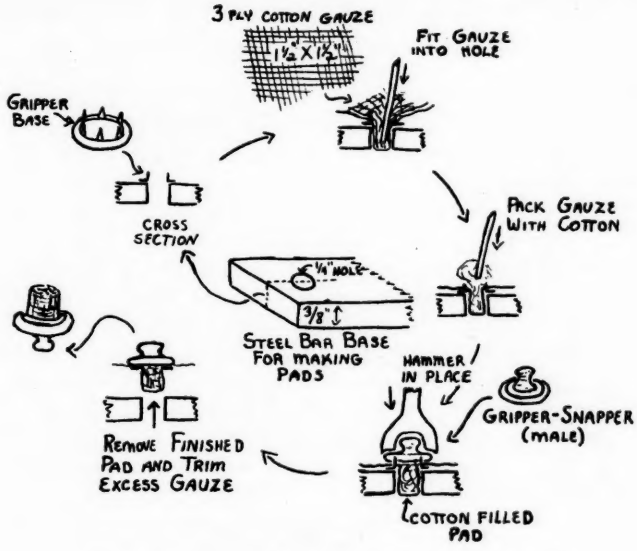

Fig. 2. Preparation of gripper-snapper electrode pad.

to receive twenty-four allergen containing testing pads. This was connected to the negative pole of a power supply consisting of two 45 volt "B" batteries connected to an ammeter and a rheostat. A grounding electrode which was wrapped in a wet towel to insure good contact was connected

to the positive pole. A current of 0.05 milliamperes was used for each testing cup or a total of 1.2 milliamperes for the twenty-four testing pads (Figs. 1, 2 and 3).

Glycerinated 1:10, 1:20, 1:33 and Aqueous 1:50 extracts pH 5.5-7.5

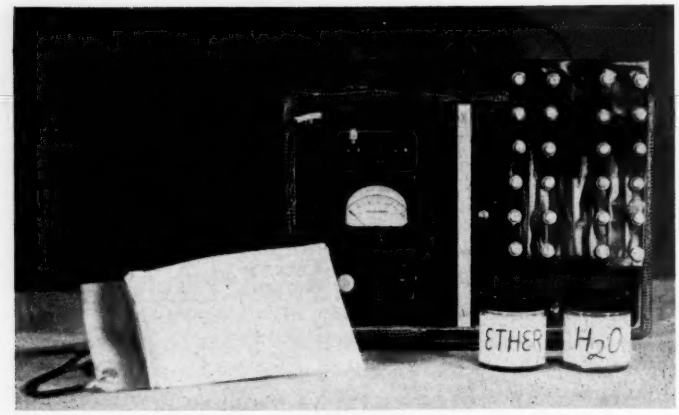

Fig. 3. (a) Positive electrode, (b) ammeter, (c) testing pad.

TABLE I. ALLERGENS USED FOR TESTS

1.	Control Pollen	
2.	Bermuda Grass	1:20
3.	Johnson Grass	1:20
4.	Orchard Grass	1:20
5.	Kentucky Blue Grass	1:20
6.	Corn	1:20
7.	Cocklebur	1:20
8.	English Plantain	1:20
9.	Giant Ragweed	1:20
10.	Short Ragweed	1:20
11.	Rough Redwood Pigweed	1:20
12.	Lamb's Quarters	1:20
13.	Burweed Marsh Elder	1:20
14.	House Dust	1:10
15.	Cat Hair	1:10
16.	Dog Hair	1:10
17.	Sheep Wool	1:10
18.	Feather Mixture	1:10
19.	Control Protein	
20.	Milk (whole)	1:10
21.	Eggs (whole)	1:10
22.	Horse Dander	1:10
23.	Crab	1:10
24.	Shrimp	1:10

Histamine (0.1 mg)—1:10
" (0.01 mg)—1:100
" (0.001 mg)—1:1000
" (0.0001 mg)—1:10,000

were tested. Some were prepared in our laboratory and some were obtained from a commercial source.* The saturated absorbent cotton plug of each gripper cup held 0.4 ml of allergen solution.

*Glycerinated extracts 1:20 supplied by Hollister-Stier Laboratories.

Technique.—The skin was prepared and the test applied in the following manner.

1. Place patient chest down with positive electrode wrapped in wet towel under chest.
2. Wash back gently with ether to remove skin oils, then moisten skin with distilled water.
3. Tape testing electrode in position, being sure that all allergen pads contact the skin.
4. Increase slowly to 0.05 milliamperes for each allergen pad and maintain for fifteen minutes.
5. Remove testing electrode and read immediately.

+—Area of simple erythema
++—Small, isolated papular hives
+++—Coalescing hives
++++—Large wheal with pseudopodia

The allergen containing electrode was left in place for fifteen minutes. After removal from the skin, the tests were read immediately. Positive tests were interpreted on the basis of the code set up by Dutton and Morse. The same observer interpreted all the iontophoretic tests in the present study, however the scratch and intradermal tests were interpreted by several observers.

CLINICAL DATA

The patients chosen for iontophoretic testing were principally those who had demonstrated relatively good skin sensitivity to the scratch tests since our main concern was to compare the two tests in children. A few children who had minimal scratch tests with normal skin, a few with excessively dry skin, and a few whose skin reacted to glycerine were included for comparison.

Approximately 1100 tests were applied iontophoretically and the reactions were compared with either those from scratch, intradermal or both methods. In the younger children, the scratch method was the only one employed. A total of sixty patients were used in this study, fifty children, and ten adults. No constitutional reactions were observed.

The age of these children was that of the general distribution of the patients seen in our allergy clinic, the youngest being eighteen months and the oldest fifteen years, with the predominant group in the four to ten-year age range. There were 65 per cent white and 35 per cent Negro patients, with twenty-eight males and eighteen females.

RESULTS

The information obtained in this study can be considered in several ways. The first concerns the choice of extract used for iontophoresis. A comparison of the relative activity of aqueous 1:50, and glycerinated 1:33 extracts of twelve different pollens, used in 532 iontophoresis tests performed on twenty-six children, shows agreement in the general pattern of

reaction in eighteen individuals. Of the eight panels of tests which were not in agreement, in four the aqueous extracts gave a larger number of positive tests or stronger tests than did the glycerine. The results in two patients could not be interpreted because of poor contact between skin and test pad in one child, and inconsistencies in the other child.

Comparison of the two types of extracts in a slightly different way shows that of the total number of tests which were not in agreement, there were more one plus reactions to aqueous than glycerinated extracts (30:17), the two plus reactions were nearly equal (21:24), and the three and four plus reactions were essentially equal (14:15).

A comparison of the relative sensitivity of the scratch and iontophoresis techniques showed one-third more positive tests by scratch than by iontophoresis of either aqueous or glycerinated material. Most of these positive tests were in those scratch reactions read as + to 2 plus, in the 3 to 4 plus range there was close agreement. The same findings held true for the comparison of intradermal (1:1000) tests with iontophoresis on the adults.

The second important consideration is the effect of different types of skin and clinical states on the reactions obtained. There were twenty-two children with 3 and 4-plus positive scratch tests. In four of these individuals, the skin was abnormally dry, and the strongest iontophoresis was 1 to 2 plus. Of the eighteen children with normal skin, fourteen were in reasonably close agreement in the tests, both in degree of reaction and the pollens reacting on the two methods. Of the four in which there was disagreement regarding the results of the two techniques, three children had stronger grass pollen reaction by iontophoresis with glycerine extracts than by scratch tests to the same material. Three of these were clinically grass sensitive, and one had had three years of grass desensitization. In the other pollens in these four children, there was close agreement in both scratch and iontophoresis results.

The depth of pigmentation of the skin did not appear to influence the iontophoretic reaction and presented no more problem in reading than it does with the scratch or intradermal methods. The number of patients tested was not sufficient for statistical differences. However, there did not appear to be a sex difference in reactivity to the iontophoretic tests. Nor did there appear to be any difference in reaction to the iontophoresis tests which could be related to clinical disease. These conditions included patients with allergic rhinitis, and asthma, alone, or combined with, allergic rhinitis and/or eczema. There did appear to be some reduction in skin sensitivity to both scratch and intradermals in those patients on antihistamines and local steroids.

A third aspect for comparison between the techniques involves the reactions of mild degree in which skin trauma is a factor. There were nine children whose maximum scratch test was 2 plus. In six, the pollens were positive by scratch test and entirely negative by iontophoresis. These

children did show positive reactions by both techniques to other inhalants. Five children receiving desensitization for pollens showed scratch tests to more pollens at this 2-plus level than by iontophoresis. It should be added that in children with 3 and 4-plus reactions no difference between scratch and iontophoresis tests could be related to desensitization.

There were six children whose maximum scratch test was plus-minus to 1 plus to any pollen, with a total of eighteen positive pollen reactions out of 108 pollen tests. These were in most instances suspected to be glycerine reactions. Of these six children, four reacted negatively to all pollens by iontophoresis. In one child, only two pollens, in another four pollens were positive by iontophoresis, compared to eight by scratch tests. In all six of these patients, house dust, feathers, wool or cat hair gave 1-3 plus iontophoresis reactions which were as strong or stronger than the same antigen applied by scratch test.

DISCUSSION

As has been reported by others who have used this technique, there were fewer positive tests with the iontophoretic[2] method, and the positive tests were easier to read than are scratch and intradermal tests. Other than a slight tingling sensation, no reaction was noted to the current, and most children and mothers preferred this method to the scratch tests. The mild to moderate tingling experienced by the children with excessively dry skin was prevented by wetting their backs with distilled water just before testing.

There was good correlation with the clinical sensitivity in about 66 per cent of patients which compares favorably with the ratio obtained by other techniques. It was not possible to prove that the fewer positive iontophoresis tests were solely the result of decreased skin trauma, although this seemed likely in the scratch reactions below 2 plus intensity. Factors pertaining to the allergen solutions themselves such as pH, polarity, concentration, or lack of potency did not seem to be decisive factors determining the decreased number of positive tests by iontophoresis.

In a few children who were known to have clinical food sensitivity, crab, shrimp, milk and egg were tested, with identical reactions by iontophoresis and scratch test. This same was true for one child with a 4-plus reaction and clinical horse dander sensitivity.

The decreased skin trauma seems to be one of the main advantages to iontophoretic method. It provides a uniformity between test sites at each testing, and between tests done at different times which may be lacking due to human variables with other methods.

One of the most important technical points in iontophoresis is a flexible testing electrode which lends itself to the various contours of the back and at the same time applies equal pressure to each of the testing pads, and insures good contact with the skin. This problem seemed to be solved by covering the thin mesh electrode screen with electrical tape only. It

was found that one could be sure of good skin contact by taping the electrode in place rather than by using sand bags to keep it in position. With small children, especially under the age of two, some sedation is helpful, while many of the older children went to sleep during the test. No infection related to the iontophoretic method was observed in the total series of tests.

The plastic cups containing cotton made as described by Morse were somewhat difficult to fill and to change. By the substitution of gripper-snappers, this was simplified. Other advantages of the grippers were uniformity of size, low cost, and better contact with the skin. They could be discarded after being used, which avoided the problem of washing the plastic cups and possible cross contamination.

The glycerinated preparations were preferred for several reasons. They did not evaporate from the pads as did the aqueous extracts, which meant that the pads stayed moist for more tests before they needed additional extracts. Approximately four tests could be carried out before the pads needed remoistening. This represents less than 0.1 ml of allergen solution per skin test. The aqueous extracts produced a more rapid response and a slightly larger number of positives, but the reaction was more diffuse and more difficult to interpret.[2] Thus the aqueous extracts did not prove to be practical for large scale testing. Depending upon the interval between tests, at least twenty tests can be applied before the pads on the electrode need changing. On several patients the abdomen as well as the chest was used as a testing location and the results were indistinguishable. We, too, found that the iontophoresis tests could be performed more quickly than scratch or intradermal tests.

CONCLUSION

Iontophoretic testing of skin sensitivity to various allergens correlates well enough with other methods to warrant more extensive use. The optimum pH for the individual allergen solutions has not been definitively answered in this paper nor is it clear from the literature. Glycerinated extracts are more practical to use than aqueous extracts. Advantages of iontophoresis are the lack of tissue trauma, speed of testing, small quantity of allergen required, uniformity of application, minimum of pain ("no needles"). The predominant disadvantages at present are lack of standards of reference, particularly for food allergens, lack of pre-fabricated testing apparatus, and inconvenience of interchanging allergens for the individual patient.

The present study demonstrates the feasibility of using the iontophoresis of allergens for routine allergy testing on pediatric patients. Furthermore it again calls attention to a non-traumatic technique for introducing material into the human skin which has potential for many different applications for both investigation of skin physiology and sensitivity.

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Department of Pediatrics (Dr. Dees)
Duke University Medical Center
Durham, North Carolina

MAKING SENSE

The study of meaning is a subject so surrounded with difficulties and contradictions that few people dare speak about it confidently. When we use a word, it has to mean the same to us as it does to the person we are addressing, or else our thoughts are not transmitted intact. Consider the meaning of meaning as it applies to some words in the medical vocabulary. There is the etymological meaning, the implicational meaning (notions either true or false upon which the etymological meaning is based), and the referential meaning. Consider the words meconium and micturition from these three aspects. Much confusion results. Once a word has been mishandled consistently, it is useless for scholars to try to preserve its correct meaning. . . . What other troubles arise from words? Consider that deceptive but convenient noun—the word "mind." Because it has been christened with a substantive, it is easy to think of it as possessing substantial size or shape or substance. The mind has no more existence than the sight, hearing, or digestion; it is much more a process than a thing. Attempts are made to partition it as if it were as solid as a boarding-house, and psychiatric architects erect jerry-built cubicles within it.—R. ASHER, Making Sense: *The Lancet*, 7099:359 (Sept. 19) 1959.

CLINICAL USE OF GLUTAMATES (CAPOMATE) IN THE TREATMENT OF RESISTANT BRONCHIAL ASTHMA

I. S. EPSTEIN, M.D.
Philadelphia, Pennsylvania

IN THE TREATMENT of bronchial asthma, a symptom which is particularly difficult to alleviate is the hard cough of the patient who cannot raise mucus. The origin of the tight, tenacious bronchial secretions is not clear nor is the best method of treating it, although many different methods have been tried to effect its removal. A method of modifying the thick elastic type of secretion was investigated by us and was reported in 1956.[1] This study is a follow-up of the clinical cases reported at that time, some of whom have been treated for five years.

In the earlier paper, we reported an effort to determine more information on the nature of the thick bronchial secretions in asthmatic patients. Flame photometric analyses were done on samples obtained by bronchoscopy from the bronchi of patients with chronic asthma. Comparable samples were obtained from patients with bronchogenic carcinoma and from patients with non-malignant lung lesions. The potassium content of the mucus, when compared on a dry weight basis, was about twice as high in the asthmatic patients as in the other patients.

The high potassium content was considered evidence of potassium loss from the bronchial cell. The loss was probably due to increased permeability or porosity of the cell wall, and the increased porosity could cause loss of other cellular elements. If the thick elastic secretions in the bronchi should come from escaping intracellular components, then the preferred method of treatment would be to decrease the permeability of the cell wall. The presence of excessive potassium in the bronchial secretions should act as an indicator for excessive permeability. This premise was presumed to be valid when clinical improvement was found to correlate with the potassium levels of the secretions. A Cofflator machine was used to obtain serial samples to avoid the trauma of repeated bronchoscopy. The machine was found to be adequate in those patients whose bronchial secretions were sufficiently voluminous.

The preparation which proved to suppress potassium levels and thus presumably to alter cell wall permeability was calcium glutamate. The calcium was selected on the basis of its potassium-sparing action[2] and glutamate because of a possible effect preventing the loss of potassium from the cell.[3] Calcium glutamate in a dose of 3 gm a day was found to effect a decrease in the potassium levels of bronchial secretions. However, the rationale for calcium did not hold up when experimental controls were run. The same amount of calcium given as the gluconate did not maintain the levels achieved by the calcium glutamate.

The effect of the latter salt is therefore probably related to the glutamate moiety of the molecule. *In vitro* work by Krebs and Eggleton[3] indicated that in brain slices potassium loss from the cell is decreased or prevented by glutamate. The premise that the glutamate alone is the effective portion has not been investigated in this study. In many ways, calcium appears to be a good choice of cation, even if it should not have good effects by itself. The calcium salt was effective; serum calcium levels were found to be unchanged by 6 gm of calcium glutamate per day (Table I). No toxicities or side effects were encountered. The analytical data on the bronchial secretions were about those which had been hoped for. Clinical improvement was slow, a factor which was anticipated if the action of the drug were to prevent further formation of thick secretions, rather than to effect its removal once it had formed. It was also observed that a moderate amount of potassium enhanced both the rate and the end point of the effect. During the past two years, treatment has been standardized with mixed potassium and calcium glutamate.

This paper has been prepared at the time when our first three patients have been under treatment with glutamate for five years. The purposes of the paper are to give a long term report of the status of the previous patients, to add a few more started since that time, and to reiterate what can be expected and what should not be expected of calcium and potassium glutamate.

Since preparation of this paper clinical substantiation of our findings has been reported by Zoss.[4]

Materials and Methods.—The patients included were those who did not respond satisfactorily to the drugs commonly used in allergology. These drugs included hyposensitizing agents, broncho-dilators, antihistamines, iodides, steroids and so forth. Those patients who were selected for this study retained asthmatic râles and exertional dyspnea in spite of vigorous treatment.

There are a total of sixteen cases in this series, ten of whom were reported on in the preceding paper. Two of the sixteen patients have died, one as reported before, and one more in the ensuing two years. Both were seventy years old or older and had severe pulmonary and cardiovascular pathology.

Three patients under glutamate therapy have been followed for five years, one for four years and five for two years or more. Seven patients have been followed for periods of up to twelve months. Two of the patients who were treated for three and four months, respectively, have been lost to the study.* All other surviving patients are still under observation.

Treatment has been continued as before, with emergency measures taken as needed. Glutamate has been added as tablets containing 350 mg calcium

*These cases represent case Number Nine of the previous study and Case Number Sixteen of the present study.

TABLE I.

Case	Age	Sex	Diagnosis	Duration of Observation		Effect on Vital Capacity		Exercise Tolerance	Serum Calcium
				Before Glutamate	After Glutamate	Average Before	After Glutamate	Before After KCG	mg/100 ml
1. M.S.	75	M	Infectious asthma, bronchiectasis	1 year	3 years			½ block 2 blocks	9.1 to 10.5
2. J.R.	70	M	Pulm. fibrosis; emphysema, infectious asthma, ASCV with cong. failure	1½ years	1 year	1250 cc	1560 cc	orthopnea 7 blocks	8.8 to 9.4
3. R.K.	42	F	Bronchial asthma, allergic rhinitis	6 months	3 years	2000 cc	2420 cc 2900 cc		10.2 to 9.6
4. B.B.	66	F	Chronic bronchitis, bronchial asthma, bronchiectasis	10 years	5 years	1380 cc	1530 cc		8.6 to 9.0
5. W.G.	35	M	Bronchial asthma	1 year	4½ years	3000 cc	3500 cc		10.2 to 11.0
6. C.C.	65	M	Bronchiectasis, emphysema, asthma, pulm. fibrosis	2 weeks	5 weeks			orthopnea	
7. J.E.	52	M	Bronchial asthma	6 months	5 years	2820 cc	3300 cc	2 blocks—qs	9.8 to 11.0
8. R.S.	36	F	Bronchial asthma	1 year	5 years			qs	
9. D.R.	55	F	Infectious asthma	2 months	3 months				
10. B.K.	74	M	Bronchiectasis, emphysema, asthma	1 month	1 month			Subjective Sl. increase—not measured	
11. F.K.	68	F	Bronchiectasis, infectious asthma	1 year	2 years			No change	
12. R.M.	48	F	Pulm. Tbc. infectious asthma	2 years	2 years			No change	
13. D.L.	64	F	Bronchial asthma, kyphosis, H.C.V.	3 months	2½ years			Slight improvement	8.8 to 9.0
14. S.N.	49	F	Infectious asthma	2 years	5 months	1950 cc	2400 cc	Increase in exercise tolerance subjectively	9.3 to 9.8
15. M.P.	68	M	Bronchial asthma, cor pulmonale, pulm. fibrosis	2 years	1 year			orthopnea at rest slight improvement subjectively	
16. L.T.	56	M	Bronchial asthma (infectious)	6 months	4 months			orthopnea	

glutamate and 150 mg of potassium glutamate (Capomate). Two tablets have been prescribed three times daily. In some patients, this dose schedule has been increased to four times a day and in others reduced to three or four tablets a day. Over the years, the patients have learned to adjust their intake upwards or downwards depending on their condition. Eight of the patients were given intermittent courses of calcium gluconate tablets for comparison with calcium glutamate. The tablets of both compounds contained equal amounts of calcium.

Results.—The data on the sixteen patients are summarized in Table I.

CASE REPORTS

CG = calcium glutamate; KCG = potassium calcium glutamate

Case 1.—Improved within three weeks on CG treatment. There was a reduction of asthmatic type râles, lessened cough, and less viscidity of sputum. There was no improvement during the upper respiratory infection with CG. KCG seemed more effective than CG. The patient relapsed on calcium gluconate placebo.

Case 2.—Improvement was noted within five days on CG. Dyspnea and wheezing lessened. He relapsed with upper respiratory infection and no improvement followed CG until KCl was added. He became more comfortable and rales almost disappeared. When CG and KCl were stopped, he relapsed within one day. CVA, terminating in death in one month, occurred a year after CG was started.

Case 3.—The placebo of calcium gluconate was ineffective but a switch to CG brought relief within a week. There was less sputum, fewer rales and less cough. Sputum was raised more easily. Orthopnea was converted to two-pillow rest at night. Has had remissions lasting up to six months.

Case 4.—CG again and again caused disappearance of sonorous sibilant rales, but not of subcrepitant bronchiectatic rales. She had steroids at times with no improvement. CG and KCG invariably lessened her cough and her thick ropy expectoration. Rales increased within a week when she was put on placebo.

Case 5.—Clinical improvement noted after CG was further enhanced by KCl. The K content of bronchial expectoration as obtained by the Cofflator showed a decrease at the time of administration of KCG and clinical improvement. Now he has periods of remission lasting from four to six months at a time. Ten days on placebo therapy was followed by a marked increase in symptomatology.

Case 6.—This man smoked three to four packs of cigarettes per day. He showed no change with a week's treatment of placebo but improved somewhat when switched to CG. He showed symptomatic improvement and a sharp drop in K content of bronchial secretions while on CG. Because of the relatively short period of observation, no conclusions can be drawn. It seems likely however that CG had some bearing on his improvement.

Case 7.—After showing gradual deterioration on one month's placebo therapy, this white male responded well to CG. Exposure to smoke and coal gas caused a flare up of symptoms and a rise in K in bronchial secretions which responded to CG. Cortisone also produced subjective improvement but not more marked than with CG.

Case 8.—This woman failed to respond to cortisone, ACTH, or hyposensitization. She responded favorably to CG and even more to KCl + CG. K content of sputum during therapy decreased. During five years of therapy, she had no toxic reactions and obtained good clinical improvement within one to two weeks of starting KCG. She had shown no improvement on placebo.

Case 9.—This woman responded to CG during her first month of treatment; however, she became depressed and agitated, and developed environmental difficulties with her daughter and grandchildren. Dyspnea and tightness of her chest persisted. She moved to Florida and was lost to further follow-up. The calcium gluconate placebo had not shown a similar beneficial effect.

Case 10.—A short obese white man was dyspneic because of asthma and marked obesity. He indulged in culinary orgies and refused to co-operate for any sustained period of time. Aside from some questionable decrease in cough and expectoration, no noticeable improvement was obtained.

Case 11.—This patient had a thick mucoid purulent productive expectoration, dyspnea, and coarse rales and constant wheezing. Vasodilators and antibiotics gave insignificant relief. KCG produced subjective improvement consisting of easier breathing, less viscid bronchial expectorations, and fewer rales.

Case 12.—This woman had a thoracotomy for moderately advanced pulmonary tuberculosis and bronchial asthma and hay fever. Hyposensitization and anti-histamines controlled her symptoms only minimally. Addition of KCG resulted in greater ease of breathing and a decrease in wheezing and respiratory discomfort and in rales. There were no toxic effects noted.

Case 13.—This obese hypertensive woman had marked kyphosis secondary to a compression fracture of D 8. Asthma became severe after a fall in which she injured her coccyx. Allergy to foods was established, but wheezing persisted despite allergen free diets. She had compensated cardiac disease. Symptomatic treatment was minimally effective. The addition of KCG increased ease of breathing and lessened her cough and wheeze. Her chest gradually cleared until she went into remission which has lasted for four months.

Case 14.—This woman had a long standing history of infectious asthma which went into remission for nine years following delivery of a normal baby. After flu vaccine, asthma recurred and became severe. Hyposensitization, IV aminophylline and steroids provided only transitory relief. KCG was started and improvement is more prolonged. She has had fewer attacks in the last three months, less wheeze, and fewer rales.

Case 15.—This patient was in constant respiratory distress from pulmonary fibrosis, cor pulmonale, and infectious bronchial asthma. He remained in cardiac compensation on digitalis but developed asthmatic flare ups with repeated upper respiratory infections. On KCG he was subjectively more comfortable; however, his long-standing pulmonary pathology is probably irreversible. There was a lessening of respiratory distress and of cough. He continued to have rales throughout both lungs, and he showed marked dyspnea with minimal exertion.

Case 16.—This white man, a heavy smoker, developed increasing shortness of breath, dyspnea, and wheezing following an upper respiratory infection. Standard remedies including steroids gave insufficient relief. KCG was added 3 to 6 gms a day without noticeable improvement. Tracheobronchitis was reported on bronchos-

copy which provided relief lasting only two days. He was again placed on metacortolone in large doses with and without KCG and aminophylline but failed to respond. To date, he is virtually disabled by orthopnea despite continuous therapy and hyposensitization.

In none of the patients was any significant change in blood pressure noted. One patient developed gastrointestinal disturbances following KCG which disappeared when CG was reinstituted. In no case did the patients respond clinically to calcium gluconate placebo.

DISCUSSION

After the patients have received glutamate for two to four weeks, the effect appears to be a decrease in the amount of thick tenacious mucus and also a liquefaction of what remains. Rales of the asthmatic type are thus decreased and control of wheeze, cough, and exertional dyspnea is made much easier.

All of the patients who have been treated with the glutamates for two years or more have stopped taking glutamates at one time or another. All but one have returned to them. Some take the tablets only at the onset of wheezing to obtain relief in three or four days. This time interval is in marked contrast to the time required for the initial effect to be seen in patients who have been allowed to relapse completely or patients started de novo on the treatment.

Regarding acute episodes, it can be said of these patients, based on observations made over the five-year period, that continuous treatment with glutamates increases their resistance and makes them responsive to treatment. Intermittent use of glutamates helps response after a time lag of several days. Without glutamates, control is very difficult to the point occasionally of requiring hospitalization and true emergency measures.

The continuous use of glutamates seems to have merit for patients with chronic asthma, particularly those who have recurrent acute attacks with every respiratory infection, with every change in weather, and with every emotional upset. The breathing of patients with marked emphysema apparently is helped if heavy mucus has cut down the respiratory airflow. Three of the four pulmonary insufficiency cripples who became orthopneic on walking across a room were able to walk much greater distances, even up to half a block, without too much distress; the fourth, case sixteen, did not respond.

Two of the more recent patients could not be controlled with the usual measures including metacortandrolone for five days, one at 20 mg, the other at 30 mg per day. The steroid was reduced and withdrawn, glutamates were started, and in each case the patient responded. But more usual is the patient with partial response to a maximal dose of steroid whose response is better and whose steroid requirements can be reduced or relegated to an emergency measure.

However, the glutamates do not do much for the patient in an acute

episode, nor for the patient with a febriie illness until the infection is controlled. This series has been limited to those patients who have not responded well to other treatment since we observed over five years ago that the effectiveness of control measures in the acute asthmatic was not influenced. No attempt has been made to give the glutamates prophylactically to recurrent asthmatics in an effort to prevent their becoming chronic patients. This might be a reasonable suggestion because continuous cellular damage from repeated acute attacks might well lead to a gradual deterioration which could be prevented by supportive measures at the cellular level. To prove this point would require a large series followed for a long period of time. Perhaps a children's asthmatic clinic would be in a position to follow it through.

SUMMARY

Sixteen chronic asthmatic patients who were resistant to treatment and who were subject to repeated flareups have been treated with calcium glutamate and with potassium for periods up to five years.

The glutamate has thinned rubbery thick secretions permitting easier coughing and raising of sputum and has decreased asthmatic rales.

There was an increased vital capacity and increased exertional tolerance even in patients with advanced pulmonary pathology.

The effect of the glutamates continues even after five years, and the patients will still relapse on withdrawal of these substances.

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5219 Lebanon Avenue

THE THINKING PROCESS

". . . we must get ready for a good job of thinking in several ways. First, by taking the right mental attitude, just as a good athlete takes a right posture. This attitude must be neutral and wide open; no *ifs* and *buts* or reservations, prejudices, preconceived convictions or emotional bias. It is a humble attitude, like that of a scientist; the attitude of keen, genuine but thoroughly impartial interest in the result of a clean, honest job of thinking. If we suspect ourselves of bias, we must be willing to discount it. We must be willing to see the thinking through to its logical end and face the truth, however unpalatable."—J. GEORGE FREDERICK, *The Will To Think*, Robert Cousins, ed., Farrar, Straus and Cudahy, New York, 1957.

TREATMENT OF ALLERGIC DISORDERS WITH METHDILAZINE

ANGELO P. SPOTO, JR., M.D., Lackland Air Force Base, Texas
and
HERBERT O. SIEKER, M.D., Durham, North Carolina

SINCE THE discovery of antergan [N-phenyl-N-benzyl-N′-dimethyl-ethylene-diamine], a large number of clinically effective antihistaminics have been developed.[5] In general, as the therapeutic effectiveness of the compounds has been increased, there has been a concomitant rise in certain undesirable side effects, particularly drowsiness. Therefore, the search for an ideal antihistamine has continued to the present time.

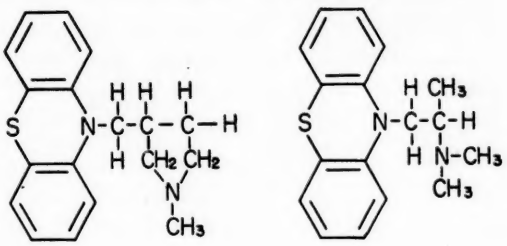

Fig. 1. Chemical formula of methdilazine.

Methdilazine®* [10-(1-methyl-3-pyrrolidymethyl) phenothiazine hydrochloride] is an antihistaminic of the phenothiazine type which has recently become available commercially. The chemical formula of this drug is illustrated in Figure 1 and shows that it is quite similar to promethozine (phenergan). In animal experiments, methdilazine was particularly effective in its ability to inhibit increased capillary permeability.[7] There was a wide margin between the dosages providing antihistaminic effects and those producing alterations in central nervous system function.[8] The drug also showed little toxicity with complete clearance from tissue in twenty-four hours after a single dose.

This study was undertaken to determine the clinical efficacy of the compound in a general allergy practice.

MATERIALS AND METHODS

Forty-five patients were selected from the allergy clinic and in-patient service at the Duke University Medical Center. The only restriction placed

From the Department of Medicine (Division of Allergy), Duke University Medical Center, Durham, North Carolina.
Dr. Spoto was a trainee, U. S. Public Health Service, Institute of Allergy and Infectious Diseases, 1958-1959.
*Supplied by Mead Johnson & Co. under the trade name Tacaryl.

upon the selection of patients was the ability to be followed closely. Observations made before starting treatment and at two-week intervals included a review of symptoms, physical examination, urinalysis, and leukocyte count. The patient's symptoms were reviewed at two-week

TABLE I. STANDARD FORM FOR DRUG EVALUATION

1. Therapeutic Result		
a. Hay Fever	b. Bronchial Asthma	c. Urticaria
Frequency of attacks Sneezing Nasal itching Nasal congestion Rhinorrhea Eye itch or burning Throat itching Other symptoms	Frequency of attacks Dyspnea Wheezing Chest tightness Cough Sputum production Other symptoms	Frequency of attacks Size of reaction Redness Itching Burning Other symptoms
2. Side Effects		3. Toxicity
Drowsiness Vertigo Fever Nausea Vomiting Diarrhea Constipation	Frequency of urination Urticaria Eczema Purpura Fixed rash Other	Depression of leucocytes Proteinuria Abnormal urine sediment Other

intervals with reference to a standard form (Table I), and the response to therapy was graded as improved, the same, or worse. Side effects and evidences of toxicity were also noted. The dosage schedule ranged from 4 mg twice a day to 8 mg four times a day with an average daily dose of 16 mg. The treatment period varied from one week to six months with an average of eight weeks.

Of the forty-five patients evaluated while receiving methdilazine, twenty-six had asthma, forty had allergic rhinitis, and six had urticaria. The patients, twenty-five males and twenty females, ranged in age from fourteen to fifty-six years. Many of the patients with asthma were receiving various other medications including aerosol and oral bronchodilator drugs and hyposensitization treatment. In those instances, the medications were continued during the trial with methdilazine.

TABLE II. RESULTS OF CLINICAL STUDY WITH METHDILAZINE

Symptoms	Improved	Same	Worse
Allergic rhinitis	31 (80%)	9 (20%)	0
Bronchial asthma	19 (73%)	6 (23%)	1 (4%)
Urticaria	2	4	0

RESULTS

The results are summarized in Table II. Of the patients with symptoms of allergic rhinitis, thirty-one (80 per cent) reported they were definitely improved, while nine (20 per cent) thought they were unchanged. None noted a worsening of symptoms. Two patients who had not previously

responded to other antihistamines were improved with methdilazine. Evaluation of six patients with urticaria revealed that two reported definite improvement and four thought they were unchanged. Of the patients with asthma, nineteen (73 per cent) noted definite improvement in symptoms related to this manifestation of their allergic disorder, while six (23 per cent) thought they were unchanged, and one (4 per cent) thought he was worse.

There was a total of thirteen patients (28 per cent) who observed side effects that could be attributed to the medication. Nine patients (20 per cent) reported drowsiness, one described vertigo, and one reported headache. These symptoms required the drug to be stopped in only one individual, however. The occurrence of drowsiness could not be related to the dose level of the drug. One patient who had experienced drowsiness with another antihistamine noted no such side effect with methdilazine. The only possible toxic reaction was observed in a thirty-five-year-old Negro man in whom a bullous pretibial rash occurred after two weeks of treatment. Other causes for the rash could not be excluded including the possibility of stasis dermatitis. The medication was stopped and the rash cleared after several days without recurrence. One patient, an anxious individual, reported the inability to remember names while on the medication. This disappeared after the drug was discontinued.

DISCUSSION

The above evidence indicates that methdilazine is an effective antihistamine. In evaluating the therapeutic response obtained, the results observed in the asthmatic patients are difficult to evaluate because of the multiplicity of medications involved. Yet, it is interesting to note that nineteen patients (73 per cent) noted improvement of symptoms while on the regimen that included methdilazine. The response to this type of drug can be evaluated best in the patient with allergic rhinitis because no other medications were used in conjunction with this antihistamine. Improvement was noted in thirty-one patients (80 per cent) of the group. These findings are similar to those obtained in other series using dimetane (hay fever, 70 per cent),[2] chlor-trimeton (allergic rhinitis, 80 per cent),[4] and pyribenzamine (hay fever, 68 per cent).[3] Two of the patients who had used antihistamines previously noted relief of symptoms of allergic rhinitis for the first time with methdilazine. One patient failed to have his usual antihistaminic drowsiness while on the drug.

Side effects encountered with the use of antihistaminics such as pyribenzamine and benadryl vary from 10 to 50 per cent.[1] Other authors state that the general overall incidence of side reactions in the therapeutic dosage range of most antihistamines is about 20 per cent.[5] From this study, side effects were noted with methdilazine in 28 per cent of patients with a 20 per cent incidence of drowsiness. The latter was measured as any degree of drowsiness and not just that amount necessary for discontinuation of

the medication. This is similar to what Thomas has found recently with dimetane.[6]

SUMMARY

Forty-five patients with allergic rhinitis, bronchial asthma, and urticaria have been treated with a new antihistamine, methdilazine. The drug was effective in 80 per cent of the patients in relieving symptoms of allergic rhinitis. There was a 28 per cent incidence of side effects with a 20 per cent incidence of drowsiness, but only one patient required discontinuation of the drug.

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ADDENDUM

Since this article was submitted for publication, the following article has appeared in print:

Wahner, H. W., and Peters, G. A.: An evaluation of some newer antihistaminic drugs against pollinosis. Proc. Staff Meet., Mayo Clinic, 35:161 (Mar. 30) 1960.

Department of Medicine (Division of Allergy) (Dr. Sieker)
Duke University Medical Center

HYPOTHESIS

Sometimes its negation brings a conclusion of obvious absurdity, and then the hypothesis is true and invariable. Or else one deduces an obvious error from its affirmation, and then the hypothesis is held to be false. And when one has not been able to find any mistake either in its negation or its affirmation, then the hypothesis remains doubtful, so that, in order that the hypothesis may be demonstrable, it is not enough that all the phenomena result from it, but rather it is necessary if there ensues something contrary to a single one of the expected phenomena, that this suffice to establish its falsity.—BLAISE PASCAL (1623-1662), *Treatise on the Vacuum.*

ANTIGENICITY OF THE WHEY PROTEINS IN EVAPORATED COW'S MILK AND WHOLE GOAT'S MILK

SIDNEY SAPERSTEIN, Ph.D.
Elgin, Illinois

IT HAS generally been accepted over the years that allergy to cow's milk is the result of prior sensitization to one or more of the proteins contained in the whey portion of the milk. A true allergic response to one or more of the casein fractions of milk has been difficult to establish with any degree of certainty, owing to the fact that a casein preparation completely devoid of whey protein contaminants has not been available. The usual commercial preparations probably have higher levels of contamination than those products produced on an experimental basis.

A number of reports and inferences, in which casein sensitivity was thought to have been established, were based on results of trial feedings, where both goat's milk and evaporated cow's milk manifested allergic responses in patients.[1,2] The results presented here indicate that conclusions drawn from such tests probably are not valid.

The objective of the present work was twofold: 1. To establish with reasonable certainty whether or not the whey proteins of commercially available evaporated cow's milk were completely denatured. 2. To study the species interrelationship of the whey proteins of cow's milk and goat's milk.

Since, at the present time, only two of the principal whey allergens have been fractionated in sufficient quantity and purity for use in such an evaluation (*beta*-lactoglobulin and *alpha*-lactalbumin), all our tests were essentially directed toward the qualitative determination of these proteins in commercial evaporated milk products. In addition, the extent of similarity of these two proteins from bovine whey was compared with their analogs in goat's milk whey by means of specific immunologic tests.

MATERIAL

The purified *alpha*-lactalbumin and *beta*-lactoglobulin were prepared by the methods of McMeekin,[3] and Gordon and Zeigler.[4] These proteins showed single electrophoretic peaks; however, slight cross contamination of these fractions can be demonstrated by using the Schultz-Dale technique.[5] This slight contamination did not interfere with our preparation of specific antisera.

The goat euglobulin was prepared according to the method of Smith[6] for cow euglobulin.

Presented at the Sixteenth Annual Congress of The American College of Allergists, Miami Beach, Florida, on March 2, 1960.

Dr. Saperstein is Supervisor of Microbiology of the Borden Special Products Company, a Division of the Borden Company.

Two samples of goat milk were used. One was obtained from a commercial distributor, the other from a single herd. No distinguishing features were noted between the two samples.

The evaporated milk represented four major brands. Samples of the various brands tested were purchased in supermarkets.

METHODS

Four white female New Zealand rabbits (5 to 6 pounds) were used for the production of each type of antiserum. The rabbits were injected subcutaneously every two or three days with 10 mg of protein (nitrogen $\times$ 6.25) for a period of five to six weeks.

The proteins for injection were prepared according to a method suggested by De Falco.[7] In essence, the method consisted of adding a sufficient volume of 4 per cent tannic acid to a 1 per cent solution of the protein, such that complete precipitation of the protein as a tannate was effected. The tannate was washed three times with distilled water and then suspended at the desired concentration using distilled water.

Following the course of sensitization, antiserum samples were collected daily by bleeding the rabbits from the marginal ear vein. Sample collection was commenced five days after the last protein injection. The antisera were tested by employing the precipitin test. These tests afforded us the opportunity of determining when antibody peaks were reached, and at this time blood was collected by cardiac puncture.

Antibodies to the whey proteins fell sharply after reaching their peak. Eight days after the last sensitizing injection was given, the antisera for these proteins was generally very weak.

The antiserum for bovine serum was obtained from the Serological Museum.*

Anaphylactic tests were performed by passively sensitizing guinea pigs (250 to 350 grs) with a single 1 ml intraperitoneal injection of the specific antiserum. The animals were challenged twenty-four to forty-eight hours later with 0.5 to 1.0 ml of solution injected into the lower cephalic vein. The dosages varied with the material being tested and are discussed with the respective tests.

The precipitin tests were conducted in the manner described by Boyd.[8] The reactions were carried out in test tubes of 10 x 70 mm. Saline of 0.8 per cent was used as the diluent for the antigens. The antisera were used undiluted. The precipitin tests were conducted at 25° C. Evaporated milk samples for the precipitin tests were prepared as follows: The milk was reconstituted by the addition of an equal volume of distilled water and then acidified to pH 4.5 to 4.6 with dilute HCl. The casein was removed from the acidified milk by centrifugation. The acid-cleared whey was readjusted to pH 6.8 to 7.0 with dilute NaOH, and the resulting phosphate

*Rutgers, The State University, New Brunswick, N. J.

precipitate was removed by centrifugation also. The goat milk was similarly cleared of casein and phosphate before testing.

In the anamnestic tests, one or two subcutaneous injections containing 10 mg of protein was given each rabbit. Blood was collected beginning on the fifth day following the last injection.

TABLE I. EVAPORATED MILK VERSUS ANTI BETA-LACTOGLOBULIN SERUM

	Antigen Dilution*					
	1/500	1/1000	1/2000	1/4000	1/8000	Control
Milk A						
Sample 1	+	−	−	−	−	−
2	+	+	−	−	−	−
3	+	+	−	−	−	−
4	+	−	−	−	−	−
Milk B						
Sample 1	+	+	+	−	−	−
2	+	+	+	−	−	−
3	+	+	+	+	−	−
4	+	+	+	+	+	−
Milk C						
Sample 1	+	−	−	−	−	−
2	+	−	−	−	−	−
3	+	+	+	−	−	−
4	+	+	+	+	+	−
Milk D						
Sample 1	+	+	−	−	−	−
2	+	+	−	−	−	−
3	+	+	+	+	−	−

*Antigen dilution based on protein content; protein nitrogen x 6.25.

Where indicated, protein nitrogen was determined by standard semimicro Kjeldahl methods.[9] All protein values are given as protein nitrogen $\times$ 6.25, where protein nitrogen is taken as the difference between the total Kjeldahl value and the non-protein nitrogen value.[9]

RESULTS

The homologous antisera produced by either *alpha*-lactalbumin or *beta*-lactoglobulin were very specific. No cross reactions were obtained when tested against heterologous antigens in the precipitin test, or in the anaphylactic tests.

In Table I, the results with anti-*beta*-lactoglobulin serum are presented. No evaporated milk sample was negative with respect to this protein. It must be remembered, however, that the extent of the reaction is not being measured quantitatively, but qualitatively. Some of the whey proteins are co-precipitated with casein after heat treatment of milk and are, therefore, not detected by our precipitin test. Nevertheless, the precipitin tests demonstrated the presence of *beta*-lactoglobulin in commercial products. Definite variations between lots was noticeable.

In Table II, the reactions of evaporated milk whey with anti-*alpha*-

TABLE II.
EVAPORATED MILK SAMPLES VERSUS ANTI ALPHA-LACTALBUMIN SERUM

	Antigen Dilution*					
	1/500	1/1000	1/2000	1/4000	1/8000	Control
Milk A						
Sample 1	−	−	−	−	−	−
2	−	−	−	−	−	−
3	−	−				−
4	+	+	−			−
Milk B						
Sample 1	+	+	−	−		−
2	+	+	−	−		−
3	+	+	−	−		−
4	+	+	+	+	+	−
Milk C						
Sample 1	+	−	−			−
2	−	−	−			−
3	+	+	+	−		−
4	+	+	+	−		−
Milk D						
Sample 1	+	−	−			−
2	−	−	−			−
3	+	+	+	+	−	−

*Antigen dilution based on protein content; protein nitrogen x 6.25.

lactalbumin serum is presented. While some samples were found to be negative, variations between lots were again noted, demonstrating the lack of uniformity in the destruction of this heat-denaturable protein.

A number of guinea pigs were passively sensitized with specific antisera to *alpha*-lactalbumin and *beta*-lactoglobulin, respectively. The animals were challenged twenty-four to forty-eight hours later using reconstituted evaporated milk, from which the fat and insolubles were removed by centrifugation. The results of these tests are shown in Table III. The challenge dose represented 7.5 to 15 mg of total milk protein. This was equivalent to approximately 0.9 to 1.8 mg of milk albumin protein. While the results show some variation, as would be expected after examination of the precipitin reactions, they were, nonetheless, positive for both of these proteins. The requisite controls were run to demonstrate that there were no nonspecific reactions. A second challenge with homologous antigen was used to test for specific desensitization. Such desensitization was found when the initial reaction was severe. In a number of instances where a weak or mild anaphylactic reaction occurred on the initial challenge, the second challenge resulted in a further response. This is not an uncommon phenomenon in the anaphylactic shock test, or in the Schultz-Dale test. The rechallenging dose was never less than 2.5 mg of protein.

No attempt was made at this time to determine the minimal sensitizing dose or the minimal shocking dose with respect to evaporated milk. This study of dosage levels is under investigation in other laboratories.[10]

In a recent study by Ratner *et al*,[11] these workers reported that heated milks such as used in commercial infant formulas were not capable of

TABLE III. ANAPHYLACTIC SHOCK TESTS*

	Sensitized To Beta-Lactoglobulin	Sensitized To Alpha-Lactalbumin
Milk A		
Sample 1	++++, +++, +++	+++, +++, ++, ++
2	++++, ++++, ++, ++	+++, +++
3	++++, ++++, +++	++, ++
4	++++, ++++, +++, ++	++, ++
Milk B		
Sample 1	+++, ++	++++, +++
2	++++	++++, +++, ++
3	++++, +++, +++	++++, +++, ++
4	+++, ++	++++, ++
Milk C		
Sample 1	+++, +++, ++, ++	+++, ++
2	++, ++, ++	++++, ++
3	++++, +++, +++, ++	++++, ++
4	+++, +++	++++, ++
Milk D		
Sample 1	+++, ++, ++	+++, +++, +++
2	++++, ++, ++, ++	++, ++, ++, ++
3	+++, ++	+++, +++, +++
4	++	++
Goat whey**	++++, +++, +++, +++, +++	++++, ++++, ++++, +++
Infant formula (liquid)	++++, ++++, +++, ++	++++, ++++, +++, ++, ++

*++++ Anaphylactic death; +++ severe anaphylaxis with collapse and recovery; ++ moderate anaphylaxis with moderate collapse and recovery; + mild anaphylaxis: scratching, coughing dyspnea; − no anaphylaxis. All animals sensitized passively with specific antiserum.

**Dose equal to 0.32 mg protein nitrogen.

eliciting an anaphylactic response for *alpha*-lactalbumin, nor did they find these milks capable of sensitizing guinea pigs to this protein. Their results, relative to obtaining negative anaphylactic shock, are not in agreement with the results presented here. Employing the same commercial infant formula described by these investigators, but challenging the animals with a tenfold increase in dose, positive anaphylactic responses were obtained in all cases for *beta*-lactoglobulin and *alpha*-lactalbumin. The results are shown in Table III. Positive precipitin tests for these two protein allergens were also obtained.

TABLE IV. GOAT WHEY VERSUS ANTISERA FOR VARIOUS BOVINE PROTEINS

Antiserum	Antigen Dilution*										
	1/500	1/1000	1/2000	1/4000	1/8000	1/16000	1/32000	1/64000	1/128000	1/256000	Control
Alpha-lactalbumin	+	+	+	+	+	+	+	+	+	−	−
Beta-lactoglobulin	+	+	+	+	+	+	+	+	+	+	−
Whey	+	+	+	+	+	+	+	+	+	+	−

*Antigen dilution based on protein content; protein nitrogen x 6.25.

To test for cross reactions between the *alpha*-lactalbumin and *beta*-lactoglobulin of cow's milk whey and goat's milk whey, high titer antisera, produced against the homologous bovine proteins, was used. Precipitin tests demonstrated that antiserum to bovine *alpha*-lactalbumin or *beta*-lactoglobulin reacted well with goat whey (Table IV). In the course of

running these precipitin tests, it was noted that antiserum to whole bovine whey reacted faster with goat whey than did the anti-*beta*-lactoglobulin serum or the anti-*alpha*-lactalbumin serum. This could be the result of (1) additive effects of the two proteins, (2) the presence of still other common antigens in the goat whey or (3) a combination of both these factors.

TABLE V. GOAT EUGLOBULIN FRACTION (IMMUNE PROTEIN) VERSUS VARIOUS ANTISERA FOR BOVINE PROTEINS

Antiserum	Antigen Dilution*						
	1/4000	1/8000	1/16000	1/32000	1/64000	1/128000	Control
Beef	+	+	+	−	−	−	−
Whey	+	+	+	+	+	−	−
Alpha-lactalbumin	−	−	−	−	−	−	−
Beta-lactoglobulin	−	−	−	−	−	−	−

*Antigen dilution based on protein content; protein nitrogen x 6.25.

To test for the presence of other common antigens, goat euglobulin (immune protein globulin) was prepared and tested against various specific antisera for bovine proteins. As seen in Table V, the goat euglobulin reacted with anti-beef serum and anti-bovine whey serum. Negative precipitin reactions were obtained with this protein and anti-*alpha*-lactalbumin serum and anti-*beta*-lactoglobulin serum, indicating a relative freedom of contamination from the two homologous proteins.

Using the recall phenomenon, it was demonstrated that rabbits which had produced no antiserum to bovine whey proteins for several months, could be induced to produce relatively high titer antiserum again, by giving them one or two subcutaneous injections of 10 mg of protein obtained from goat's milk whey (Table VI).

As a final test, several guinea pigs were passively sensitized by intraperitoneal injection of antiserum for bovine *alpha*-lactalbumin and *beta*-lactoglobulin, respectively. The animals were then challenged with 2 mg goat whey protein. Definite anaphylactic responses were elicited as shown in Table III. The immunologic similarity between goat and cow *alpha*-lactalbumin and *beta*-lactoglobulin was thus clearly demonstrated by these tests, *i.e.*, precipitin, anamnestic and anaphylactic.

DISCUSSION

The utilization of electrophoretically pure *alpha*-lactalbumin and *beta*-lactoglobulin in the immunological tests under investigation, revealed the presence of these two important allergens in commercial samples of evaporated milks. The use of such purified protein preparations has also led to the discovery of an immunologic similarity between these proteins, as they occur in cow's milk, and as their respective counterparts occur in goat's milk.

TABLE VI. ANAMNESTIC REACTIONS

Antiserum*	Antigen (Bovine)	Antigen Dilution**										
		1/200	1/400	1/800	1/1600	1/3200	1/6400	1/12800	1/25600	1/51200	1/102000	Control
Rabbit 1	Alpha-Lactalbumin		+		+		+		+		+	−
2			+		+		+		+	+	+	−
3		+		+		+	−	−				−
Rabbit 1	Beta-Lactoglobulin	−		−		−	−					−
2***					+		+		+	−		−
3		−		−		−	−					−
Rabbit 1	Whole casein	−		−		−	−	−				−
2		−		−		−	−	−				−
3		−		−		−	−	−				−
Rabbit 1	Whey		+		+	+		+				−
2			+		+	+		+				−
3			+		+	+		+				−

*Antiserum produced following single injection of goat's milk whey equivalent to 0.8 mg protein nitrogen.
**Antigen dilution based on protein content; protein nitrogen x 6.25.
***Two injections.

There is also evidence for a degree of immunologic interrelation between the immune proteins of goat's milk and the immune proteins of beef serum. The immune proteins of bovine milk and bovine serum are indistinguishable.[3,6]

In the earlier studies on milk protein reactions reported by Versell,[12] cross reactions between goat and cow milk could not be clearly interpreted as being the result of any one specific protein. The reason for this was that heterogenous antigens were used in his experiments. Likewise, the report by Hill[13] on various skin tests utilizing fractions from goat and cow milks is not definitive in the light of our present knowledge of the protein composition of these milks.[3] Even as recently as 1959, a publication by one allergist[2] stressed the species specificity of goat's milk whey and cow's milk whey.

The assumption that a milk allergic subject is sensitive to casein is no longer valid, or at least highly questionable, if it is based solely on the clinical evidence that neither evaporated cow's milk nor goat's milk is tolerated. Although there is a reduction in what is considered to be the principal whey allergens, *alpha*-lactalbumin and *beta*-lactoglobulin, concomitant to the production of evaporated milk, a significant quantity of these allergens still remains in the final product. Since individual sensitivity is known to be a variable factor in milk allergics, this residual amount of whey protein may be sufficient to cause an allergic response.

In the report of Ratner *et al*[11] mentioned earlier, a positive anaphylactic response to *alpha*-lactalbumin was not obtained when guinea pigs were challenged with a heat treated infant milk formula. Since the same authors demonstrated in an earlier report[14] that *alpha*-lactalbumin was a poorer antigen than *beta*-lactoglobulin, it is likely that their animals did not reach a sufficient degree of sensitization prior to challenge. Also, their challenge dose of 0.1 ml of this milk, having a total protein level of 1.7 per cent, may

have been too low to elicit a response. The authors alluded to such a possibility in their report. A product such as they described would contain approximately 0.05 mg of *alpha*-lactalbumin in the challenge dose if no heat denaturation had taken place. It is readily seen, therefore, that their challenge dose was extremely small.

Alpha-lactalbumin is a weak antigen and its sensitizing power can be enhanced if injected with an adjuvant.[5,15] In the present work, it was found that the use of highly active specific antisera for passive sensitization in place of active sensitization, gave more reproducible results in the anaphylactic tests.

Perhaps one factor which has led several investigators to erroneously conclude that evaporated milks contain no whey allergens is the instability of the whey proteins to moist heat.[16] In an excellent study of the stability of milk proteins to heat, Jenness[17] clearly demonstrated that under certain conditions *beta*-lactoglobulin is denatured by heat. This, however, does not negate the fact that proteins show varying degrees of heat stability, depending upon the presence or absence of other substances,[18] as well as the concentration of these substances.

If there are true milk allergic subjects who can tolerate goat's milk and not evaporated cow's milk, our interpretation would certainly lie in the direction of postulating the presence of allergens other than *alpha*-lactalbumin and *beta*-lactoglobulin in the latter. The results presented here lead this writer to conclude that an allergy to bovine *alpha*-lactalbumin or *beta*-lactoglobulin cannot be treated by substitution of goat's milk for cow's milk. Neither is it likely that evaporated cow's milk could be used in such instances, unless there exists only a very low level of sensitivity in the individual.

There are in bovine milk, several proteins which have not been prepared in pure form, or the quantities prepared are, as yet, insufficient for adequate immunological or clinical test purposes. Among these are the lipoproteins, the eu- and pseudoglobulins (immune proteins), and the components III and V which appear on electrophoretic patterns.

The presence of other allergens bound to the milk proteins should not be overlooked. The milk proteins are capable of combining with a variety of substances. These substances are not readily freed from the proteins, and if allergens, are likely to elicit a response of their own.

It is readily seen that further work on this problem may clarify some of the conflicting reports which have appeared in the literature. As further refinements in biochemical and biophysical techniques are made, it is likely that our knowledge relative to milk allergy, as well as allergy in general, will be advanced.

SUMMARY

Two principal whey allergens of cow's milk, *alpha*-lactalbumin and *beta*-lactoglobulin, are not completely destroyed in the preparation of evaporated

milk. The presence of residual amounts of these proteins can be demonstrated by the tube precipitin test and by the gross anaphylactic shock test.

The previously accepted belief that there is a species specificity between the whey proteins of goat's milk and cow's milk was not substantiated. Antisera produced against bovine *alpha*-lactalbumin and *beta*-lactoglobulin react with the analogous proteins of goats' milk whey. Moreover, antisera to bovine whey and bovine serum react with the euglobulin fraction of goat's milk.

ACKNOWLEDGMENT

The author is indebted to Drs. W. G. Gordon and T. L. McMeekin of the U. S. Department of Agriculture for making available the purified samples of *beta*-lactoglobulin and *alpha*-lactalbumin.

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A DOUBLE BLIND STUDY OF ISOPROPHENAMINE IN CHILDHOOD ASTHMA

ERNEST M. HEIMLICH, M.D., RAFAEL C. HARRIS, M.D., F.A.C.A.
and ROBERT E. SMITH, Capt. USAF (MC)
Los Angeles, California

ISOPROPHENAMINE (1-0-chlorophenyl-2-isopropylaminoethanol) has been reported to be an effective oral bronchodilator in animals[1] and in adult asthmatic patients.[2] Isoprophenamine is a sympathomimetic amine related to epinephrine, isoproterenol and ephedrine. The present report is a double blind study to evaluate the effectiveness of this drug in the prophylaxis of bronchospasm in asthmatic children.

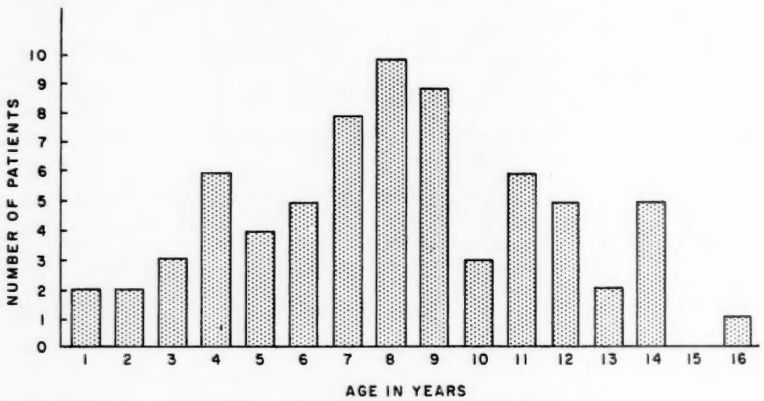

Fig. 1. Age distribution of patients.

MATERIALS AND METHODS

Seventy-one asthmatic children, one and one-half to sixteen years of age, were given 293 random weekly trials of Syrup of Vortel® (Isoprophenamine and ethoxybutamoxane hydrochloride, Lilly) and a placebo syrup.* The average and mean age of the patients was eight years (Fig. 1). The patients were on the study from one to ten weeks with an average and mean of four weeks (Fig. 2). The patients were all known asthmatics treated for a minimum of two months prior to the study. The majority received hyposensitization prior to and during the study. All had bronchospasm in the

From the Department of Pediatrics, School of Medicine, University of California at Los Angeles; Harbor General Hospital, Los Angeles, and Orange County General Hospital, Orange, California.

*Supplied as "Vortel" by Dr. J. G. Armstrong, Lilly Laboratories for Clinical Research, Indianapolis, Indiana.

baseline week before being placed on the study, and all had been receiving medications ranging from simple expectorants to corticosteroids. During the study, no medication apart from the experimental drug was given except when symptoms became so severe that other medication (primarily adrenalin injections) was deemed imperative.

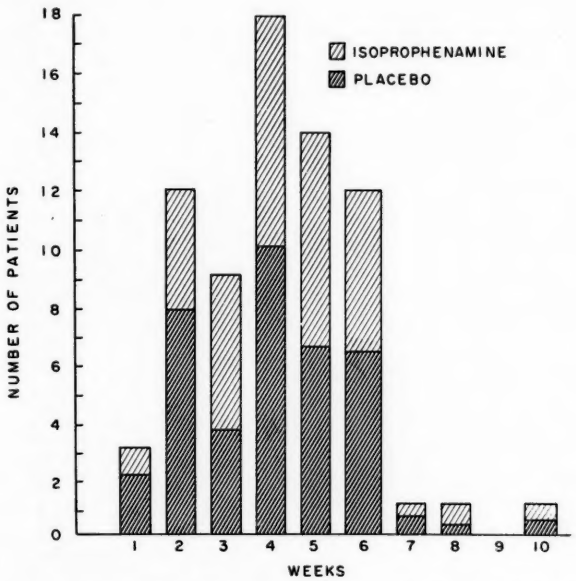

Fig. 2. Distribution of patients as to number of weekly trials.

Daily doses of Isoprophenamine ranged from 15 mgm (5 mg tid) to 80 mgm (20 mg qid), depending on the age and size of the patient as recommended by the manufacturer (Fig. 3).

One of us (RCH) dispensed number coded medications, examined the patients weekly and kept weekly records. Each patient kept a daily record of symptoms and medications used, which was given to the recording physician weekly. A different member of the team (RES) tabulated the results recorded on the charts without knowing either the patients or the nature of the medications. After all results were recorded and tabulated, the medication code was broken.

RESULTS

Patients were evaluated weekly by history concerning the frequency, duration and severity of asthmatic symptoms, and possible side effects of the drug. They were also given a weekly physical examination for signs of bronchospasm.

Their symptoms and signs were classified in relation to the baseline week as "worse" (Isoprophenamine 11 per cent, placebo 9 per cent), "unchanged" (Isoprophenamine 34 per cent, placebo 35 per cent), "improved" (Isoprophenamine 23 per cent, placebo 22 per cent), and "asymptomatic"

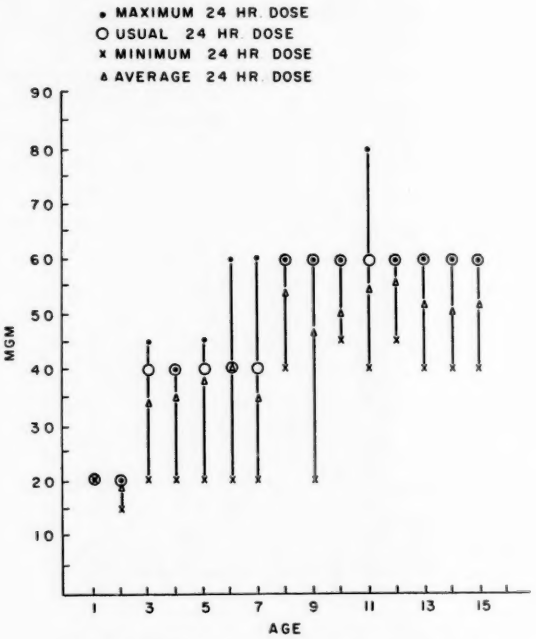

Fig. 3. Twenty-four hour dose range by age.

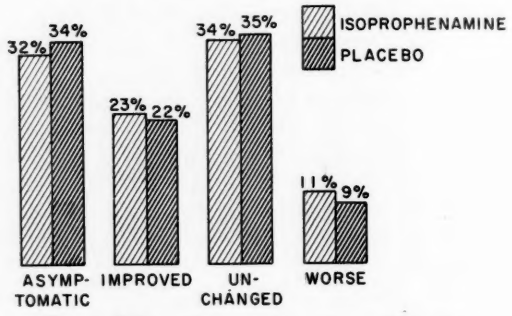

Fig. 4. Effects of isoprophenamine and placebo.

(Isoprophenamine 32 per cent, placebo 34 per cent) (Fig. 4). No difference in relief or prevention of symptoms was observed between the active material and the placebo. No side effects were observed in any of the trials.

DISCUSSION

We are unable to account for the difference between our results and the previous animal and adult findings. It may be due to dosage level, since Johnston and Shipley found a marked difference in the effect on maximal expiratory flow rate produced in asthmatic adults by 20 mgm and 30 mgm per dose, respectively.[2] Moreover, central nervous system stimulation has been consistently recorded as a side effect in previous adult studies. Since this symptom was not observed in our patients, this may indicate inadequate dosage level in the present study. Our method of evaluation, based primarily on subjective evidence rather than on objective data such as pulmonary function studies, may not have been sufficiently critical. Further studies are projected.

SUMMARY

A double blind clinical study to evaluate the effectiveness of Isoprophenamine in the prophylaxis of bronchospasm in seventy-one asthmatic children revealed no difference in relief or prevention of symptoms between the active material and the placebo.

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Department of Pediatrics (Dr. Heimlich)
University of California Medical Center
Los Angeles 24

CAUSES OF ERROR

"Now there are four chief obstacles in grasping truth which hinder every man, however learned, and scarcely allow anyone to win a clear title to learning; namely, submission to faulty and unworthy authority, influence of custom, popular prejudice, and concealment of our own ignorance accompanied by an ostentatious display of our knowledge. Every man is entangled in these difficulties, every rank is beset. For people without distinction draw the same conclusion from three arguments, than which none could be worse, namely, for this the authority of our predecessors is adduced, this is the custom, this is the common belief; hence correct."—ROGER BACON, *Opus Majus,* English translation by Robert Belle Burke, Philadelphia, 1928.

PROBABLE ROLE OF BLOOD VOLUME ALTERATION IN ANGIOEDEMA

A Case Report

BEN R. FISCH, M.D., O. C. E. HANSEN-PRUSS, M.D., F.A.C.A., and H. O. SIEKER, M.D.
Durham, North Carolina

URTICARIA and angioedema have been reviewed in medical literature[1-4] with discussions of almost every aspect of their etiology and therapy. Similarly, many complications[5-10] of the disorders have been reported. Blotner,[11] in 1942, described a patient who developed angioedema leading to shock. The patient was found to have hemo-concentration as shown by repeated red blood cell counts and hemoglobins. No hematocrit values were reported. It was suggested that this condition was similar to that seen in surgical shock, and the patient was treated with intravenous saline solution and epinephrine injections. Raynolds,[12] in 1943, reported a similar case which he treated with intravenous plasma. In a recent review with an extensive bibliography by Sheldon, Mathews, and Lovell,[13] we were unable, however, to find observations or comments regarding the blood volume and its alteration in angioedema.

This is a report of a case of recurrent angioedema with repeated bouts of peripheral circulatory collapse, which were probably secondary to the loss of fluid into the extravascular space and resultant blood volume depletion.

CASE REPORT

The patient, O. B., a fifty-nine-year-old white man, was first seen by the Allergy Department of Duke University in 1954. A history was obtained of recurrent bouts of urticaria characterized by short-lasting pruritic wheal formation, since childhood, which the patient was unable to relate to any specific factors. In 1939, following the ingestion of twelve Alka-Seltzer tablets, he developed a generalized urticaria which progressed to angioedema, and subsequently, for the first time, he became very weak and fainted. He was not sure of the sequence, but believed that as the symptoms lessened (in a few hours) the weakness gradually abated. This did not recur until 1952, when he received three penicillin tablets, orally, for an upper respiratory infection, over a twelve-hour period. Within fifteen hours after taking the first tablet, the patient developed severe, generalized, pruritic urticaria which was associated with weakness and momentary loss of consciousness. He related that he was in "shock" with unobtainable blood pressure or pulse and was treated with injections of caffeine and adrenalin. Six weeks later, after chewing a sulfathiazole tablet, he had a similar episode. Again, several months later, after ingestion of two aspirin tablets the symptoms recurred. Several times over the next two years he had similar experiences without any apparent cause.

He was first admitted to Duke Medical Center in 1954 for a diagnostic work-up.

Dr. Fisch is Instructor in Medicine, Dr. Hansen-Pruss is Professor of Medicine and Dr. Sieker is Associate Professor of Medicine, Duke University Medical Center, Durham, North Carolina.

Family history was negative for allergy except for one sibling who had developed a contact dermatitis from exposure to merthiolate. His initial examination was essentially normal, except for slight obesity, enlarged tonsils and adenoids with epithelial debris in the crypts, and chest findings consistent with minimal emphysema. Accessory clinical findings were normal. These included hemoglobin, hematocrit, white blood count and differential, urinalysis, bromsulphalein test, thymol turbidity, electrocardiogram, and sinus, chest, gastrointestinal and gallbladder x-rays. An electroencephalogram showed no abnormality. It was the opinion that the patient's symptoms of syncope were due to a vasodepressor response in a setting of angioedema.

By means of skin tests, the patient was found to be allergic to several common grasses, dust, kapok, cat hair, rhizopus, and several foods, including citrus fruits, cheese, and chocolate. Scratch patch tests were positive to sulfacetamide and procaine penicillin. A culture was obtained from the nose and throat, and an autogenous vaccine was prepared from this source.

He was discharged with instructions to take antihistamines if needed for recurrences of the angioedema and atropine, whenever necessary, for the symptoms of faintness. A tonsillectomy was advised to remove the focus of infection in the throat, but the patient declined this procedure at that time. He was started on a course of hyposensitization and autogenous vaccines and was placed on a reduction diet with instructions to eliminate from his diet those foods to which he was found allergic by skin test and history.

Over the next eighteen months he did well, noting no recurrence of the more severe angioedema. He was next seen at Duke Hospital in June, 1956. At that time the examination was essentially as previously described, and the vaccine therapy was continued.

He was readmitted in October, 1957, with influenza and an exacerbation of the angioedema which the patient related to the ingestion of excessive amounts of orange juice. On admission, with the more acute manifestations of the angioedema, the hematocrit was 49.5 per cent. The urine revealed a specific gravity of 1.027 with many hyaline and a few finely granular casts, and the NPN was 42 mgs per cent. No urinary symptoms were noted at any time. The allergic symptoms were easily controlled by antihistamines and atropine. As the acute angioedema subsided, the hematocrit dropped from 49.5 per cent to 40 per cent, and the renal findings cleared.

The patient's third admission was in November, 1957. He had received a sulfa drug for several days as treatment of an upper respiratory infection, and subsequently developed severe abdominal pain, angioedema, and oliguria. Initial laboratory examination revealed an hematocrit of 40 per cent, and urinalysis showing one-plus protein, many red blood cells, and sulfa crystals. He was treated for the recurrent angioedema and the acute renal retention due to ureteral blockage by sulfa crystals. Two days after his admission, when the angioedema had subsided and the urine output had returned to 1475 cc per twenty-four-hour period, the hematocrit was 34 per cent. At the time of discharge, twelve days later, the hematocrit had returned to 38 per cent, and the urinalysis was negative for protein. No cells or casts were found in the sediment.

The patient did well over the next several months except for a number of recurrences of angioedema with associated weakness, nausea, and faintness. There was no apparent cause for these attacks. On two occasions, he was hospitalized by his local physician and treated with intravenous nor-adrenalin and corticosteroids because of recurrent shock which occurred with the severe bouts of angioedema. During remissions, he continued taking antihistamines, atropine, and the vaccine treatments, but the recurrences became more severe and frequent.

In June, 1958, he returned for his fourth Duke Hospital admission for the tonsillectomy recommended initially. On admission the routine physical examination was essentially negative, except for large ragged tonsils and slight obesity. Hemo-

globin was 15.8 gms per cent, hematocrit was 45 per cent, and the urinalysis was negative. The surgical procedure was performed without incident; approximately twelve hours following surgery, and six hours after receiving 60 mgs of Codeine and 0.6 gms of aspirin, the patient developed an acute, generalized, urticarial rash which rapidly progressed to severe angioedema. Treatment with intravenous antihistamines did not control the symptoms. The patient was pallid, and the pulse and blood pressure were unobtainable. He was given 0.5 cc of epinephrine intravenously, and the blood pressure slowly rose to normal limits. As the cardiac rate increased from 40 to 80 per minute, the pulse was again obtainable, and there was a slight decrease in the angioedema. During the following four hours, he had two abrupt occurrences of itching with rapid progression to severe angioedema with shock. This appeared while he was receiving Solu-Cortef by slow intravenous drip with ACTH gel intramuscularly. He received epinephrine, intravenously, with partial clearing of the uriticaria and instantaneous rise in blood pressure.

Seven hours later the patient had his fourth episode of severe angioedema with giant wheal formation over the trunk. This was associated with a rapid pulse, hypotension, nausea and vomiting. These symptoms and findings did not respond to epinephrine or to intravenous nor-adrenalin and sterioids administered over the ensuing three hours. The pulse remained in the 110-120 range, and the blood pressure fluctuated between 80/70 to 120/100 with very narrow pulse pressures. The patient's hemoglobin was found to be 21 gms per cent as compared to 15.9 gms per cent at the time of admission. Because of the hemoconcentration, the nor-adrenalin and steroids were discontinued, and the patient was given three liters of 5 per cent glucose in normal saline over the next nine hours, which stabilized the blood pressure and pulse at normal levels. The hematocrit obtained following the rapid fluid replacement was 51 per cent. In this twenty-four-hour period, the urine output was only 75 cc. A gradual clearing of the angioedema occurred over the next two days, with an hematocrit of 45 per cent the following day and 39 per cent at the time of discharge eight days later. During this eight-day period the patient had no further episodes of angioedema or blood pressure fluctuations.

He was continued on antihistamines and Banthine for several weeks and then these medications were discontinued. He was continued on hyposensitization and autogenous vaccine therapy as previously outlined, and was told to abstain from known allergens, especially aspirin and similar products. Over the last eighteen months the patient has done well with no further symptoms of angioedema or shock reported to date, and he has continued on vaccine therapy alone.

DISCUSSION

Since its first conception as an allergic manifestation in the early 1900's, much has been written about the probable cause of urticaria and angioedema. To date, no specific single etiologic factor has been presented which does not necessitate the inclusion of other predisposing, or concomitant conditions, such as pre-existent allergic disorders, psychiatric tendencies, infections, endocrine imbalances, malignancies, or physical states.[14-19] Lewis[20] originally presented the concept of the liberation of an H-substance causing the triad of venule and capillary dilatation, increased capillary permeability, and arteriolar dilatation by antigen-antibody reaction. However, the entity of cholinergic urticaria[21] as such must be considered in any discussion of angioedema and urticaria. Grant, Pearson and Comeau[22] were the first to describe and investigate this condition and concluded that it was caused by the liberation of acetyl choline by efferent peripheral

nerves. This substance was then said to provoke the release of the H-substance in the skin because of the sensitivity of the skin cells to acetyl choline. Hopkins[23] and others,[24] have shown the subcutaneous injection of choline-like products could cause generalized urticaria in sensitive individuals, but not in people without previous urticarial history. This reaction was found to be blocked by atropine and other parasympathomimetic drugs. It was postulated by Graham and Wolf[25] that the skin reaction could be explained as an action of the acetyl choline alone. They interpreted the end result as due to the over-dilatation of the capillaries with resultant increase in their permeability as this dilatation progressed. More recently Morgan[26] substantiated the work of Lewis, Grant, *et al,* by injecting histamine-liberating agents into local skin areas, theoretically, to exhaust them of histamine. These substances stopped the occurrence of angioedema and urticaria in this local site, in the face of generalized skin reactions elsewhere. He also found that cholinesterase levels were lower than normal in three patients studied, and he postulated that this might be a potentiating factor of the acetyl choline effect in the initial stage of the reaction.

From an extensive review of the literature, no investigative work could be found which showed the effect on blood volume of serum loss through the capillary system in angioedema. However, in 1937, Black and Kemp[27] reported studies of blood density in allergic reactions. They showed that the instillation of ragweed pollen into the nose of a sensitive person produced typical hay fever symptoms and also caused an almost immediate rise in blood density. This is a rise in red blood cell concentration, or a loss of plasma from the circulation; expressed in terms of present-day hematology this would be reported as a rise in the hematocrit. They also found that with guinea pigs the blood densities increased as the degree of anaphylactic reactions became more severe.

This case report emphasizes a seldom recognized complication of severe angioedema. The recurrent bouts of fainting and probable transitory circulatory collapse that occurred for at least the six years prior to his last admission were probably allergic anaphylactoid reactions with bradycardia, hypotension, and the symptoms of shock. However, in view of the last episode of shock in which marked hemoconcentration was observed, it is suggested that the decreased circulatory blood volume may account for, or contribute to, shock in severe angioedema. In this situation, recognition of the important role of decreased circulatory blood volume should be emphasized. The volume deficit must be corrected by the administration of adequate amounts of fluids. This observation also suggests that more exact measurements of blood volume in such cases are indicated. Such investigations may elucidate the role of a change in blood volume in the symptomatology and pathophysiology of angioedema and urticaria.

SUMMARY

A case of recurrent angioedema with giant wheal formation is reviewed. Two types of shock were observed. One type was typical allergic ana-

phylactoid in origin with bradycardia, hypotension, and syncope. The other was associated with serum loss into the tissues in the presence of giant wheal formation, characterized by tachycardia, syncope, and hemoconcentration. The recognition of this type of shock in severe angioedema is important in order that specific treatment with necessary fluid replacement can be undertaken.

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Department of Medicine (Dr. Fisch)
Duke University Medical Center

CAUSATION OF ECZEMA, URTICARIA AND ANGIONEUROTIC EDEMA BY PROTEINS OTHER THAN THOSE DERIVED FROM FOOD: STUDY XVIII

(Historical Document)

I. CHANDLER WALKER, M.D.
Boston, Massachusetts

IN 1912, Talbot and Towle[1] from a study of the stools of eczematous patients, concluded that foods played a considerable part in the causation of eczema; the fats and starches as well as the proteins were concerned. In 1916, Blackfan[2] called attention to the association of eczema with asthma in children who were sensitive to foods. McBride and Schorer[3] found that in predisposed persons certain food proteins caused urticaria and erythema. White[4] noted the anaphylactic phenomenon in eczema, and a year later[5] (1917) he no longer doubted the fact that food constituents (protein, fat and carbohydrate) play some role in the abnormal composition of individuals afflicted with chronic rebellious eczema. Urticaria following the ingestion of certain foods and the injection of serum is a common occurrence. Since it would seem to be an established fact that foods may and do cause eczema and urticaria in some persons, cases illustrating such instances will not be given here. Suffice it to say that in our study of bronchial asthma we have frequently observed the association of eczema with asthma in patients who were sensitive to various food proteins, and we have definitely proved in some cases that urticaria was caused by food proteins.

In this paper I shall present instances in which eczema, urticaria and angioneurotic edema were produced by proteins which are not foods, but with which persons intimately come in contact throughout life, and which so far have not been recognized as possible causes of these conditions: four cases of eczema, two of which were caused by proteins of horse dandruff, one by the pollen of timothy and one by the pollen of ragweed; five cases of urticaria, two of which were caused by horse dandruff proteins and three by ragweed pollen, and three cases of angioneurotic edema, caused, respectively, by timothy pollen, flaxseed and ragweed pollen. With the exception of one patient who had hay fever, all of the patients had bronchial asthma, and the asthmatic condition was caused

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From the medical clinic of the Peter Bent Brigham Hospital.

This is the eighteenth of a series of papers on the study of bronchial asthma made possible through a gift by Mr. Charles F. Choats, Jr., of Boston to the Peter Bent Brigham Hospital. The papers previously published are: Studies I-V, Jour. Med. Research, 1917, *35*, 373, 391, 487, 509; Studies VI-VIII, Jour. Immunol., 1917, *2*, 227, 237 243; Study IX Am. Jour. Bot., July, 1917; Studies X-XIII, Jour. Med. Research, 1917, *36*, 231, 237, 243, 295; Study XIV, ibid., *36*, 423; Study XV, ibid., 1917, *37*, 57; Studies XVI and XVII, ibid., 1917, *37*, 277, 287.

by the same proteins that also caused the eczema, urticaria, and angioneurotic edema.

PROTOCOLS OF PATIENTS WITH ECZEMA

Case 1.—W. P., aged eleven, had bronchial asthma and eczema continuously since he was one year old. He could not ride behind a horse without having asthma. The eczema was dry and scaly, and was present all over his body with the exception of his face.

Cutaneous reactions were positive with the pollen of ragweed and with the proteins of horse dandruff. The alkali metaprotein and the peptone of horse dandruff gave positive reactions in a dilution of 1:1,000, and the coagulated protein gave a positive reaction in a dilution of 1:10,000.

The patient was treated subcutaneously at weekly intervals with gradually increasing amounts of horse dandruff coagulated protein in a dilution of 1:100,000. After a few such treatments the patient noticed that when he bathed there was much less desquamation all over his body, and his forearms were practically free from eczema. Riding behind horses no longer caused asthma.

Case 2.—M. T., a girl, aged fifteen, had bronchial asthma for nine years. Although she had asthma all through the year, it was worse in summer, when she also had hay fever. She had eczema of the hands every summer.

Cutaneous tests were positive with ragweed pollen in a dilution of 1:5,000, and with horse dandruff peptone in a dilution of 1:1,000.

After a series of treatments with ragweed pollen in gradually increasing amounts, the patient had no asthma, hay fever or eczema during the ensuing summer. Following the completion of the ragweed treatments, a series of subcutaneous injections with horse dandruff peptone were given. During twelve weekly injections of the peptone in a dilution of 1:10,000, no untoward symptoms were noted. The dilution of the peptone was then increased to 1:1,000, and each week the amount of this dilution was slowly increased. After a few of these treatments the patient began to have eczema on her forehead; this gradually spread and resisted all medication. It was thought advisable to omit treatment with the peptone and all medication for the eczema. After one week there was marked improvement in the eczema, and two weeks later the eczema had practically disappeared.

Case 3.—C. S., a girl, aged ten, had asthma since she was two years of age. The patient had eczema continuously between the ages of one and two, and she had had it off and on ever since.

Cutaneous tests were positive with the proteins of horse dandruff in dilutions of 1:10,000 and with the pollen of timothy in a dilution of 1:500.

The patient was treated subcutaneously fourteen times in as many weeks with horse dandruff alkali metaprotein, first a 1:100,000 dilution, later a 1:10,000 dilution and finally a 1:1,000 dilution being employed. During this treatment the patient was free from symptoms, including asthma and eczema. In anticipation of the pollen season, the patient was given during April and May subcutaneous injections of timothy pollen, first in a dilution of 1:1,000, then 1:500 and finally in a dilution of 1:100; this was in conjunction with the horse dandruff treatment as outlined above. After five doses of the timothy pollen, the patient complained of very troublesome eczema, which was similar to what she had had previously. She said that it began to appear after the third timothy injection, that it was gradually getting worse, and that it was the most marked the next day after the injection. The eczema was very itchy, scaly and dry, and it was present on the

back and under the knees and at the bends of the elbows in the antecubital fossae. Further injections with the timothy pollen were discontinued, but the horse dandruff treatment was continued. The eczema gradually disappeared; in two weeks the patient's back was free from eczema, and in four weeks the knees and arms became free. The patient was still being treated with large doses of horse dandruff protein.

Case 4.—A woman, aged sixty-five, always had bronchitis and eczema periodically; the eczema appeared each year during the latter part of the summer, and at this time she had bronchial asthma.

Cutaneous tests were positive with ragweed pollen only.

Previous to the cutaneous tests the patient's physician had considered ragweed pollen as a cause of eczema in this case, since she was free from it, provided she kept out of her garden which was surrounded by ragweed. After the positive test had been obtained with ragweed pollen, the patient was allowed to go in her garden with her hands and arms covered with cloth. In spite of this protection, during the latter part of August when the ragweed pollen is being shed, the patient had a little eczema. She was then not allowed to go into her garden at all, and the eczema entirely disappeared for the remainder of the summer.

In the first case there would seem to be little doubt that horse dandruff played a part in the causation of eczema, since improvement in the eczema was quite rapid during treatment with small amounts of horse dandruff protein. The same was also true of the asthmatic condition. Judging from our experience with Case 2, we should anticipate that sooner or later when large amounts of horse dandruff protein are given an amount will be reached which will make the eczematous condition worse. In Case 2 there can be no doubt that the subcutaneous injections of horse dandruff protein caused the eczema, since it appeared during the treatment and since it disappeared when the injections were discontinued. Small amounts of the protein, however, did not cause eczema; therefore it may be possible to treat eczema satisfactorily with very small desensitizing doses of the offending protein. The two cases represent two different channels of exposure to the protein; the first patient had eczema from natural exposure to horse dandruff, and the second patient had eczema when the protein was introduced beneath the skin. In other words, in the first case the offending agent was outside the body, and in the second case it was inside the body, thus simulating food in the causation of eczema.

In Case 3 there can be no doubt that timothy pollen protein caused eczema, since the eczema appeared during subcutaneous injections of the pollen, it was worse soon after each injection, and it disappeared soon after the injections were omitted. Horse dandruff proteins played no part in the causation of eczema, since injections of these proteins were continued while the eczema was clearing up. It is quite probable that previous attacks of eczema were caused by exposure to timothy pollen. In Case 4 it is quite evident that ragweed pollen caused eczema through natural exposure by contact with the pollen.

PROTOCOLS OF PATIENTS WITH URTICARIA

Case 5.—F. I., a boy, aged seven, had bronchial asthma since he was eight months old.

Cutaneous tests were positive with horse dandruff peptone and coagulated protein in dilutions of 1:10,000, and they were doubtfully positive in a dilution of 1:100,000.

The patient was given at weekly intervals six subcutaneous injections with horse dandruff peptone in a dilution of 1:1,000,000; the amount of this dilution was increased with each treatment, and no untoward symptoms resulted. The dilution of the peptone was then increased to 1:100,000, and no symptoms followed 0.1 cc of this dilution. A week later the same dose was repeated, and in a few hours the patient developed large, white, very itchy urticarial wheals over his whole back; these persisted for only a few hours. A week later the same dose was again repeated but without symptoms, and since then the amount of the dilution has been gradually increased without producing symptoms, and the patient has been free from asthma.

Case 6.—M. S., a girl, aged thirteen, had bronchial asthma since she was one year old. During the first year of age she had eczema, but this disappeared when asthma began. The patient had urticaria after drinking milk.

Cutaneous tests were positive with the proteins of rice, milk, and mackerel, and with all three proteins of horse dandruff in dilutions of 1:100, and with the coagulated protein in a dilution of 1:1,000.

The patient was given subcutaneously 0.1 cc of the coagulated protein in a dilution of 1:10,000. The next morning there were present all over her body raised, itching blotches which the patient's mother called hives. A week later the same dose was repeated without producing symptoms, and further increase in the dose produced no symptoms.

Case 7.—W. P., a man, aged forty-four, had asthma for fifteen years and hay fever for ten, both chiefly in the summer months, from the middle of August to the first of October. He had winter bronchitis.

Cutaneous tests were positive with the pollen of ragweed in a dilution of 1:5,000, and of goldenrod in a dilution of 1:100; higher dilutions of these pollens failed to give reactions.

The patient was thus treated subcutaneously at weekly intervals with ragweed pollen: 1:10,000 dilution, 0.1 cc; 1:5,000 dilution, 0.1, 0.2 and 0.3 cc; 1:1,000 dilution, 0.1 and 0.2 cc, and 1:500 dilution, 0.1 and 0.2 cc. A few minutes after the last injection, large, raised, white very itchy wheals appeared over the patient's whole body; they disappeared in a few hours. Subsequent weekly injections of 0.2 and 0.4 cc of ragweed pollen in a dilution of 1:500 caused no untoward symptoms.

Case 8.—J. M., a boy aged twelve, had asthma since he was one year of age. He had eczema from infancy up to a few years ago, when it disappeared and has not since returned.

A subcutaneous injection of 0.1 cc of a 1:1,000 dilution of ragweed pollen was followed the next morning by urticarial wheals over the whole body. Three days later, 0.1 cc of a 1:500 dilution of the pollen was followed the next morning by a much less extensive urticaria. Subsequent injections at three-day intervals of 0.2 cc of a 1:500 dilution of the pollen caused no untoward symptoms. A series of injections with the proteins of horse dandruff also failed to produce urticaria.

Case 9.—B. S., a housewife, aged forty-six, had the summer type of hay fever and asthma for nine years.

Cutaneous tests were positive in a dilution of late pollens. Timothy pollen was positive in a dilution of 1:100 and doubtful in a dilution of 1:500, red top pollen was doubtful in a dilution of 1:100 but only slightly positive in a dilution of 1:500.

The patient was given a series of subcutaneous injections at weekly intervals with timothy pollen in dilutions of 1:500 and 1:100 without symptoms. The patient was then similarly treated with ragweed pollen in 1:1000 dilution, 0.1, 0.2 and 0.3 cc, and in 1:500 dilution, 0.1 cc, without producing untoward symptoms. A week later, 0.2 cc of 1:500 dilution was followed in a few hours by an attack of asthma and by urticaria which continued for only a few hours. Treatment, however, was continued as previously with 0.3 and 0.4 cc of a 1:500 dilution and with 0.1 cc of a 1:100 dilution without producing symptoms.

In the foregoing protocol the first two patients, Cases 5 and 6, both developed urticaria following subcutaneous injections of horse dandruff proteins. It is difficult to explain why in Case 5 the second dose of 0.1 cc of protein caused urticaria when only a week previous the same dose had failed to do so. The theories of antianaphylaxis would not seem to obtain in such a case. Rackemann[6] has recently reported an instance in which such theories failed. The other three patients, Cases 7, 8, and 9, developed urticaria following injections of ragweed pollen. In Cases 7 and 9, the theories of antianaphylaxis fail. Although such experiences are neither usual nor serious, nevertheless, great care should be employed in attempting to desensitize patients in order to avoid more serious results. It is interesting that in Case 9 timothy pollen should fail to produce urticaria, whereas ragweed pollen did cause urticaria, since the patient by skin reaction was equally sensitive to the two pollens.

PROTOCOLS OF PATIENTS WITH ANGIONEUROTIC EDEMA

Case 10.—A physician, aged twenty-eight, had the summer type of hay fever for seven years, and during the past winter he had slight asthmatic attacks with colds. The patient's mother had hay fever, and his two children had urticaria after eating strawberries and lobster.

Cutaneous tests were positive with all of the common pollens and with alcoholic extracts of horse dandruff and guinea-pig hair. Timothy pollen gave a positive test in a dilution of 1:1,000 but no higher.

The patient had no ill effects following two subcutaneous injections of timothy pollen in a dilution of 1:5,000. A week later by mistake he injected 0.1 cc of a dilution of 1:500 instead of 1:1,000 as he should have done. Following this injection the patient had the following symptoms, which will be given in detail since he observed himself closely: Ten minutes after the injection, the patient's eyelids itched severely. This was quickly followed by suffusion of the face and neck; the latter rapidly became much swollen, necessitating the rapid removal of the patient's collar. The nares and nasopharynx became greatly swollen, thus making respiration through them difficult. His face became turgid and swollen, and the swelling of his face was so marked that it was on a level with his nose. The swelling of the eyelids closed his eyes. The suffusion extended rapidly over his chest and body, with intense itching, and shortly urticarial wheals developed. The

wrists and hands soon became involved, but the arms and legs remained free from wheals.

All of the foregoing symptoms, with the exception of the edema, disappeared in three hours. A few hours later, the patient had intense cramplike pains in the abdomen, and extreme tenesmus which was not relieved by going to stool. During this train of symptoms the patient's pulse rate was 120 per minute, his temperature was normal, and his respiration was rapid and labored; his blood pressure was not taken. He had considerable headache throughout the night, and he was restless and irritable. The next morning his face and eyelids were still badly swollen, and he felt somewhat prostrated, although he was not prevented from working.

Case 11.—A nurse, aged twenty-eight, had bronchitis and asthma from childhood, Recently while making a flaxseed poultice the patient had an attack of coughing, sneezing, watering of the eyes, and asthma.

Cutaneous tests were positive with the protein of flaxseed.

The patient was given subcutaneously 0.1 cc of a 1:10,000 dilution of flaxseed protein. Five minutes later the patient began to cough and choke, and five minutes later still she was unable to walk because of extreme dyspnea. Her head became very hot, her neck began to swell so that she had to quickly remove her collar, her face became so swollen that both eyes were closed, and she began to itch terribly. Her head itched severely, her ears felt like bursting, her heart felt queer, she was sick at the stomach, respiration was difficult, and on the whole she felt impending death. She was very cyanotic, and urticarial wheals developed over the upper part of her body. The urticaria soon disappeared from the upper part of the body only to appear over the lower part of the body; but in an hour she was free from urticaria. During the height of the disturbance a subcutaneous injection of epinephrin (adrenalin chloride, 1:1,000 Parke, Davis & Co.) relieved the head and earache and the dyspnea. The patient was unable to sleep because of severe gas pains in the abdomen. The next morning she felt normal.

Case 12.—F.V., a woman, aged forty-four, had asthma for seventeen years only in the summertime from the middle of August to the first of October. In childhood she had hay fever and eczema.

Cutaneous tests were positive with ragweed pollen in a dilution of 1:500, and a dilution of 1:1,000 gave a doubtful reaction.

The patient was given a subcutaneous injection of ragweed pollen in a dilution of 1:500, and a dilution of 1:1,000; 0.1 cc was given. A few minutes later she had an attack of sneezing, wheezing, ringing of the ears, running of the eyes and nose, and her face suddenly became swollen and her collar had to be quickly removed. A few hours later she was normal.

In the foregoing protocols, Patients 10 and 11 had typical angioneurotic edema, which, according to Osler, includes urticaria and intestinal cramps. In Case 10, angioneurotic edema followed too large a subcutaneous dose of timothy pollen, and in Case 11 it followed a very small dose of flaxseed protein; in fact, the amount of flaxseed protein was probably much less than that which may be readily absorbed from its application as a poultice. It is probable that the patient became sensitized to flaxseed protein through the frequent application of such poultices, since as a child she remembers such medication for her bronchitis. Patient 12 had marked

swelling of the face, neck and throat following a small injection of ragweed pollen, but the reaction was much less marked than in the two preceding cases. Such experiences well illustrate the great care that should be employed in the desensitization of persons with proteins to which they are sensitive.

CONCLUSIONS

The proteins of horse dandruff, ragweed and timothy pollens may cause eczema both from external exposure and internal injection in predisposed persons. As we have found it to be with food proteins, so it is with the foregoing proteins: Eczematous patients tolerate very small doses of the offending protein and the eczema seems to improve; but a slight increase above this small amount makes the eczema worse. The amount of protein that benefits eczema is too small to prevent asthma, and the amount of protein that benefits asthma makes the associated eczema worse. Therefore, desensitization for eczema, if such is possible, must be a very slow and cautious process, even more than for asthma.

Since small subcutaneous injections of the proteins of horse dandruff and ragweed pollen caused urticaria in some cases, it would seem advisable, when determining the cause of urticaria, to exclude all protein substances with which the patient may come in contact, as well as the food proteins. The same reasoning would seem to apply to cases of angioneurotic edema.

During the desensitization of patients with proteins, the appearance of eczema, urticaria or angioneurotic edema should make one suspect that the treatment was the cause of such symptoms. Although such experiences are not serious, yet they are sufficiently alarming to warrant great care in the desensitization of patients with proteins.

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Gonzenbach, R.: Serious infections following local hydrocortisone therapy. Schweiz. med. Wochnschr., 89:656-659 (June 20) 1959.
In three patients, cellulitis, and in two, infectious arthritis followed and may have been caused by treatment with hydrocortisone.

Sung-Ts'e, Lu, and Ch'uan-Chen, Li: Exfoliative dermatitis due to antimony potassium tartrate. A case report. Chinese M. J., 78:456 (May) 1959.
Illuminating Case Report. Initial treatment with ACTH resulted in complete resolution which took almost three months.

Cooke, R. A., Mitchell, W. F., Brown, E. A., Sherman, W. B., and Chase, M.: Single repository injection treatment of hay fever. Proc. New York Allergy Soc., New York State J. Med., 59:1816 (May 1) 1959.
Panel discussion by Drs. Mitchell, Brown, Sherman, and Chase, moderated by Dr. Cooke.

Aronson, P. R.: Hyperventilation from organic disease. Ann. Int. Med., 50:554 (Mar.) 1959.
Excellent review of organic causes of hyperventilation. All must be excluded before final diagnosis is established.

Bringhurst, L. S., Byrne, R. N., and Gershon-Cohen, J.: Respiratory disease of mushroom workers. J.A.M.A., 171:101-104 (Sept. 5) 1959.
New clinical disorder of unknown etiology as observed in sixteen Puerto Rican migratory workers.

Kautz, H. D. (Sec., Council on Drugs): Penicillin and other antibiotics in milk. Report of the Council. J.A.M.A., 171:135-137 (Sept. 5) 1959.
Concludes, "On the basis of available evidence of its oral allergenicity, such further measures as may be required to completely eliminate penicillin from the milk supply should be undertaken by the U. S. Department of Health, Education and Welfare. The elimination of other antibiotic contaminants of milk, although desirable, appears to be less urgent."

PAPERS OF INTEREST

Bedell, G. N., and Seebohm, P. M.: Treatment of pulmonary emphysema. J.A.M.A., 169:1699-1702 (Apr. 11) 1959.
When primary emphysema is differentiated from emphysema caused by other types of pulmonary disease then infections need rigorous treatment and the patient must be kept comfortable by medication.

Floch, M., and Leibowitz, S.: Hemmorrhage from multiple sites associated with chlorpromazine-induced jaundice. J.A.M.A., 170:2060-2064 (Aug. 22), 1959.
Treatment with Vitamin K_1 reversed hydrothrombinemia due to toxicity and hemorrhage in a sixty-six-year-old woman who for seventeen days had taken 75 mg daily.

Cohen, T.: Hypokalemic muscle paralysis associated with administration of chlorothiazide. J.A.M.A., 170:2083-2085 (Aug. 22) 1959.
Hypokalemia subsequent to use of drug resulted in muscular weakness and paralysis noted in left thigh and right arm.

Johnston, D. H., and Cornish, A. L.: Acute pancreatitis in patients receiving chlorothiazide. J.A.M.A., 170:2054-2056 (Aug. 22) 1959.
Following daily doses of 0.15 to 1.0 g. of chlorothiazide for two to three months, three women patients developed acute pancreatitis, possibly due to drug.

Lecca, G. G., Terry, J., Maggiolo, L., and Morales, A.: Ototoxicity of kanamycin. Report of three cases. J.A.M.A., 170:2064-2068 (Aug. 22) 1959.
In those patients treated for less than three weeks, a severe and apparently permanent loss of hearing was noted.

Milner, F. H.: Skin testing in diagnosis on allergic conditions. Allergie und. Asthma, 4:242-245, 1958.
Among the general population in Great Britain, approximately 70 per cent give positive reactions to allergens, although only ten per cent show clinical signs of allergic disease. Dermal tests are of diagnostic significance only in correlation with the patient's history.

Prausnitz, C.: Past and present: the passive transfer in allergy. Muench. med. Wochenschr., (Munich), 100:1313-1316, 1958. (In German.)
Lecture on history and present state of the passive transfer in allergy.

Levin, S. J.: Hyposensitizing (immunizing) inoculations in hay fever and asthma. Pediat. Clin. North America, 6:693-708 (Aug.) 1959.
General review.

Drerup, A., Alexander, W., Lumb, G., Cummins, A., and Clark, G. M.: Jaundice occurring in a patient treated with chlorothiazide. New England J. Med., 259:11, 534 (Sept. 11) 1958.
Generalized pruritus began four days after the first dose of chlorothiazide jaundice appearing in two weeks. Studies led to a diagnosis of intrahepatic obstructive jaundice, of which no other cause was found.

Lachman, S. J.: Anaphylactic reaction to oral chlortetracycline. Med. Proc., 4:578 (Aug. 23) 1958.
The reaction was brought under control by Benadryl given intravenously and followed by ACTH gel.

Gross, P., Gitlin, D., and Janeway, C.: The gamma globulins and their clinical significance. III. Hypergammaglobulinemia. New England J. Med., 260:3, 121-125 (Jan. 15) 1959.
Lists the disorders associated with hypergammaglobulinemia and discusses the role played by gamma globulins.

Rorsman, H.: Basophil leukocytes in asthma, atopic dermatitis, and psoriasis. Acta Dermato.-Venereol., 38:3, 175, 1958.
The average number of basophil leukocytes present in the peripheral blood of twenty patients with asthma, thirty with atopic dermatitis, and twenty-two with non-erythrodermic psoriasis did not differ from the average seen in ninety-six controls.

Prigal, S. J.: Allergy, infection, and the psyche. New York J. Med., 58:20 (Oct. 15) 1958.
A master review of present-day concepts of allergy, infection, and psychologic factors in the allergic disorders.

Stryker, H., Siegel, B., and Grolnick, M.: The allergenicity of erythromycin. AM & CT., 5:723-725 (Dec.) 1958.
The immediate, severe reaction of the hypersensitivity type does not follow the administration of erythromycin. Mild, delayed responses do occur, but their incidence is small.

Painter, T. S., Korst, D.: Studies on acquired hypogrammaglobulinemia. New England J. Med., 260:1, 15-21 (Jan. 1) 1959.
The occurrence of infectious asthma in a patient with hypogammaglobulinemia is reported.

Alexander, J. K., Misi, J., Dennis, E., Herschberger, R. L.: Effects of racemic epinephrine inhalation in cardiopulmonary function in normal man and in patients with chronic pulmonary emphysema. Circulation, 18:2, 235-248 (Aug.) 1958.
The cardiopulmonary effects following epinephrine inhalation are compared in normal and emphysematous subjects in order to evaluate differences between inhalational and parenteral administration.

Schofield, F. W.: Bee sting allergy and desensitization. A report of cases and review of the literature. Canadian M. A. J., 78:412 (March 15) 1958.
Report of five cases of allergy to bee stings, which were desensitized with a "bee body extract." One patient, following several months of treatment, was stung by a bee seventeen months later, and died.

Parnes, V.: The site of antibody formation in the body. Problems Hematol. & Blood Transfusion, 2:370, 1957.
Macrophage and lymphocyte cells all take part in antibody formation.

Uhr, J. W., and Pappenheimer, A.: Delayed hypersensitivity. III. Specific desensitization of guinea pigs sensitized to protein antigens. J. Exper. Med., 108:891 (Dec. 1) 1958.
Guinea pigs sensitized to protein antigens can be completely and specifically desensitized by a single injection if the dose of corresponding antigen is sufficiently large.

Eisen, H. N., and Tabachnick, M.: Elicitation of allergic contact dermatitis in the guinea pig. The distribution of bound dinitrobenzene groups within the skin and quantitative determination of the extent of combination of 2,4-dinitrochlorobenezene with epidermal protein *in vivo*. J. Exper. Med., 108:773 (Dec. 1) 1958.
About 99 per cent of 2,4-dinitrochlorobenzene is found in the epidermis. The rest, localized in the deeper part of the epidermis, specifically evokes the allergic response.

Sulman, F. G.: Augmentation of antihistaminic effect of diphenhydramine. Arch. Intern. Pharcacodyamine, 117:237 (Oct. 1) 1958.
Tranquilizing agents, including hydroxyzine hydrochloride (Atarax), phenothiazines, meprobamate, phenoglycodol, and benactyzine, augment the protective effects of diphenhydramine (Benadryl) against lethal doses of histamine.

Uhr, J. W., and Brandriss, M.: Delayed hypersensitivity. IV. Systemic reactivity of guinea pigs sensitized to protein antigens. J. Exper. Med., 108:905 (Dec. 1) 1958.
Hypepiesia and leukopenia follow injection of desensitizing dose of antigen in guinea pigs with the delayed type of hypersensitivity.

Metzger, F.: Further observations of climatic treatment of hay fever and asthma with special reference to Florida. Ohio State M. J., 54:10, 1312 (Oct.) 1958.
Some allergic patients are helped by climatic change. The percentage can be increased if all factors are considered before advice of change of climate is given.

In Memoriam

SION W. HOLLEY, M.D.

Dr. Sion W. Holley, M.D., died on June 8, 1960, in Farmingdale, New York, at the age of fifty-four.

Dr. Holley graduated from Baylor University with an A.B. degree in 1927. He attended the University of Chicago Medical School from 1928 to 1935—receiving a Ph.D. in pathology and an M.D., in 1935. He was instructor in pathology at Baylor University College of Medicine in Dallas, Texas, from September, 1957, to May, 1959. He served as staff physician at the Nassau County Tuberculosis Sanatorium in Farmingdale, New York, from May, 1939, through October, 1941.

In October, 1941, he entered the U. S. Army Medical Corps where he was assigned to the Army Institute of Pathology, Washington, D. C. From there he was assigned to Ft. Sam Houston, Texas (Brooks General Hospital) and in July, 1942, was re-assigned to Fitzsimons General Hospital, where his work was composed mostly of surgical pathology.

After his military service, he returned to Nassau County Sanatorium, where he became staff physician in the Tuberculosis Sanatorium. In July, 1947, he moved to Colorado, where he was in charge of anatomical and clinical pathology for the Weld County Hospital and later was pathologist to the Larimer County Hospital in Fort Collins, Colorado. During these years, he was in part-time clinical practice in Greeley and in Loveland, Colorado.

In June, 1951, he returned to his work at Nassau County Sanatorium, where he continued in private clinical practice along with his work in the County Sanatorium.

Dr. Holley was a man of unlimited energies. He was always ready and more than willing to help his fellow man and he will be greatly missed by his many friends and associates.

Dr. Holley became a member of The American College of Allergists in 1952.

J. W. H. Rouse

CONNOLLY JAMES MALLOY, M.D., F.A.C.A.

Connolly James Malloy died in Montreal on February 1, 1960, after a brief illness at the age of fifty-five.

Dr. Malloy was a graduate of McGill University, where he obtained his B.A. and in 1935 his M.D. degree. He interned at the Royal Victoria Hospital and at the Children's Memorial Hospital in Montreal. He served in the Canadian Army during World War II. He was an Assistant Physician at the Royal Victoria Hospital and a Lecturer at McGill University.

He was a Fellow of the American Academy of Allergy, the Royal College of Physicians, the International Association of Allergology, the American College of Physicians, a member of the Canadian Medical Association and the American Association for the Advancement of Science.

He was actively interested in the Canadian Academy of Allergy and was interested in the founding of the Association of Allergists of the Province of Quebec, of which he was the Vice-President.

Dr. Malloy was a man with wide literary interests, which were reflected in his publications. He was a kindly man, a friend to his patients and colleagues. He is

survived by his widow, two daughters and a son, to whom the College extends its condolences.

Dr. Malloy was promoted to Fellowship in The American College of Allergists in 1946.

M. J. MESSINGER, M.D.

CUTHBERT B. YOUNG, M.D.

Dr. Cuthbert B. Young, internist, died March 17, 1960, at his home in Tyler, Texas.

Dr. Young was born November 27, 1907, at Graham, Minnesota, and received his preliminary education in the Royalton (Minnesota) public schools. He was graduated from the University of Minnesota, where he received both his Bachelor of Science and Bachelor of Medicine degrees.

His medical degree, which had been delayed by illness, was awarded to him in 1937 by the University of Minnesota Medical School. He interned at Minneapolis General Hospital, Minneapolis.

He moved to Tyler in 1937, serving for five years as school physician. Opening his private practice in 1943, Dr. Young was staff physician at Mother Frances Hospital and Medical Center Hospital and was consulting physician at the East Texas Tuberculosis Hospital.

A member of the American Medical Association and the Texas Medical Association, Dr. Young had served as president of the Smith County Medical Society in 1958. He was a Fellow of the American College of Chest Physicians, a member of the American Trudeau Society, a member of the board of directors of the Texas Tuberculosis Association (1939-1946), and a charter member of the Smith County Tuberculosis Association. He belonged to Phi Chi medical fraternity.

In addition to his medical services, for several years he had served on the Tyler School Board. He had been a receipient of the distinguished service key award of the Junior Chamber of Commerce for his participation in the establishment of a Tuberculosis Clinic in Tyler.

He is survived by his wife, Mrs. Vivian Young, Tyler; his son, John, Tyler; two daughters, Mrs. Patricia Cain, Dallas; and Mrs. Yvonne Hyde, Austin; his mother, Mrs. Anna Young, Park Ridge, Illinois; a brother, Homer Young of San Luis Obispo, California; three sisters, Miss Olive Young, Portland, Oregon; Mrs. Irene Auker, Foley, Minnesota; and Mrs. Lucille Phinney, Park Ridge, Illinois; and two grandchildren, Polly Lou Cain and Randall Scott Hyde.

Dr. Young became a member of The American College of Allergists in 1957.

WILLIAM C. GRATER

TO QUESTION ALL THINGS

To question all things;—never to turn away from any difficulty; to accept no doctrine either from ourselves or from other people without a rigid scrutiny by negative criticism; letting no fallacy, or incoherence, or confusion of thought, step by unperceived; above all, to insist upon having the meaning of a word clearly understood before using it, and the meaning of a proposition before assenting to it:—these are the lessons we learn from ancient dialecticians.—JOHN STUART MILL.

News Items

ALLERGY FOUNDATION OF AMERICA

A grant of $37,500 to the Allergy Foundation of America for the production of a public service motion picture on allergy was presented recently by Francis C. Brown, president of Schering Corporation, to Dr. Charles D. Marple, the director of the Foundation.

The animated film, in color will present discussion of the causes of allergy, the importance of the allergic disorders and the types of tests and methods of treatments available to patients. The film will caution patients regarding self-medication.

THE ASSOCIATION OF ALLERGISTS FOR MYCOLOGICAL INVESTIGATIONS, INC.

The Association of Allergists Mycological Investigations, Inc., will hold its meeting for 1961 in conjunction with the meeting of the American College of Allergists at the Statler Hilton Hotel in Dallas, Texas. The tentative time set for the scientific section is Tuesday evening, March fourteenth. Reports of current studies and various aspects of allergy to molds will be discussed.

MICHIGAN ALLERGY SOCIETY

The Michigan Allergy Society announces the election of the following officers for the year 1960-1961:

President.....Robert G. Lovell, M.D.
Vice President.....Alex S. Friedlaender, M.D.
Secretary.....Hilda M. Hensel, M.D.
Treasurer.....Israel Wiener, M.D.

MIDWEST ALLERGY FORUM

The annual meeting of the Midwest Allergy Forum will be held at the Penn Sheraton Hotel, Pittsburgh, Pennsylvania, October 22 and 23, 1960.

The program will include a panel discussion on Chronic Urticaria, Drug Allergy and Repository Therapy in addition to presentations on Bronchial Asthma.

WASHINGTON STATE SOCIETY OF ALLERGY

New officers of the Washington State Society of Allergy for 1960 are as follows:

President—Robert F. E. Stier, M.D., Spokane, Washington
Vice President—Albert G. Corrado, M.D., Richland, Washington
Secretary-Treasurer—J. W. Georges, M.D., Seattle, Washington

BOOK REVIEWS

PROGRESS IN THE BIOLOGICAL SCIENCES IN RELATION TO DERMATOLOGY. Arthur Rook, Editor, 480 pages. Great Britain: Cambridge University Press, 1960. Price, $15.00.

In his foreword, J. S. Mitchell says, "Since the days of Harvey and Glisson, one of the characteristic features of British medicine has been the integration of medical science with clinical practice. In medicine today, the well-founded practical approach combined with human kindness is needed perhaps more than ever. With emphasis on this background, it is essential for us to take part in, and utilize the development in the University of the School of Post-Graduate Medical Teaching and Clinical Research is rendered possible by the foundations laid as a result of the remarkable achievements in the fundamental sciences."

Among the forty-two contributors to the symposium are represented internists, anatomists, pathologists, radiologists, biochemists, microbiologists, pharmacologists, histochemists, physiologists, geneticists, psychiatrists, and dermatologists. Discussed in the light of multi-disciplinary approaches are (1) Melanocyte and Melanogenesis, (2) Cutaneous Innervation, (3) The Histochemical Investigation of the Skin, (4) Bacteriology and Mycology, (5) Psychophysiological Mechanisms, (6) Comparative Medicine, (7) Immunology, (8) Inflammation, (9) Radiation of the Skin, (10) Pharmacology.

Of particular interest to allergists in the field of dermatology is the presentation by Coombs, Parrish, Gell, and Bruce, who respectively write on "Immune Phenomenon in Relation to the Skin," "Autosensitization to Skin," "Mechanisms of Dermal Hypersensitivity," and "Tuberculin Hypersensitivity."

The chapter on "Psychological Mechanisms" includes remarks by Davis on "Psychological Mechanisms in Psychosomatic Disorders" and Cullen on the "Psychological Mechanisms in the Psychosomatic Skin Affections." Witlock gives "A Critical Assessment of the Psychosomatic Concept Applied to Dermatology," and Ackner writes on "The relationship between Anxiety, Alerting, and Cutaneous Vasomotor Activity." Bradley writes on "The Mode of Action of Tranquillizing Drugs," and Magnus "Testing Patients for Photosensitivity."

Schacter's presentation of "Endogenous Substances Capable of Producing Some Features of the Acute Inflammatory Reaction," reviews histamine, 5-hydroxytryptamine, and a group of polypeptides (kallidin, bradykinin, et cetera) derived from plasma or serum, and called plasma kinins. The references given in the bibliography for this chapter are unusually well chosen, as of the end of December, 1958. The chapter on "Autosensitization to Skin" by Parrish and that on "Mechanisms of Dermal Hypersensitivity" by Gell are particularly well written and illuminating.

Mention of these particular chapters and authors is not to be taken to signify that the reader will not discover interesting relationships in other portions of the book. For example, the chapter on "The Principles of Histochemistry" by Everson Pearse includes as good a history of the subject and a classification of histochemical methods as will be found anywhere. The reader who is looking for more will find it in the author's "Lectures on the Scientific Basis of Medicine" in the series published by the University of London. This book gathers together a great deal of material which has been widely scattered throughout the literature in a number of disciplines. The lively discussions bring them together and put them into proper perspective.